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Focal Epilepsy: Correlation of the Pathological and Radiological Findings[1]

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FROM THE STANDPOINT of diagnosis and treatment the epilepsies may be divided into two groups, symptomatic and cryptogenic. In many cases the cause is readily recognized or may be reasonably assumed (for example, brain tumor, post-traumatic scars of the cerebral cortex, eclampsia, or uremia). There remains, however, a considerable group in which no cause has yet been found. Many of these cases will fall into the clinical classification of "essential" or "idiopathic" epilepsy and may show a characteristic spike and slow-wave pattern on the electrographic tracing. It is this group that has been termed cryptogenic, meaning "of obscure origin." In these cases the condition is usually familial.

Classification of each case should be attempted on both an anatomical and an etiologic basis, in accordance with Tables I and II. The latter table is by no means complete but does list the common causes which must be kept in mind during the investigation of any case of epileptic seizures. In addition, the age of the patient at the onset of the seizures will help focus attention on lesions of certain types. The commonest causes of habitual seizures beginning in infancy, for example, are birth injuries, degenerative lesions, and congenital abnormalities.

TABLE I: EPILEPTIC SEIZURES: CLINICAL AND ANATOMICAL CLASSIFICATION

(*From Penfield and Erickson*)

Clinical Type	Localization
SOMATIC MOTOR	
1. Generalized seizure (grand mal)	Complete motor
2. Jacksonian seizure (local motor)	Pre-rolandic gyrus
3. Masticatory seizure	Lower rolandic
4. Simple adversive seizure	Frontal
5. Tonic postural seizure (decerebrate, opisthotonic)	Brain stem
SOMATIC SENSORY (Auras)	
6. Somatosensory seizure	Post-rolandic gyrus
7. Visual seizure	Occipital
8. Auditory seizure	Temporal
9. Vertiginous seizure	Temporal
10. Olfactory seizure	Infratemporal
VISCERAL	
11. Autonomic Seizure	Diencephalic
PSYCHICAL	
12. Dreamy state seizure	Temporal
13. Petit mal	
14. Automatism (ictal and post-ictal)	
15. Psychotic states (secondary)	

EXPANDING LESIONS

Intracranial tumors of infancy and childhood do not often cause seizures because they are most often cerebellar in location. For seizures beginning between thirty-five and fifty-five years of age, however, neoplasms are the second commonest cause. Penfield, Erickson, and Tarlov (8)

[1] From the Montreal Neurological Institute and Childrens' Memorial Hospital, Montreal, Canada. Read in part at the Thirty-Third Annual Meeting of the Radiological Society of North America, Boston, Mass., Nov. 30–Dec. 5, 1947.

TABLE II: ETIOLOGIC CLASSIFICATION OF THE EPILEPSIES

(*From Penfield and Erickson*)

		Produced by
A.	WITH DEMONSTRABLE CEREBRAL LESIONS	
1.	Expanding lesions	Neoplasms, abscesses etc.
2.	Cerebral cicatrix	Trauma, infection
3.	Local cerebral atrophy	Compression, infection
4.	Local microgyria	Infantile compression or ischemia
5.	Brain cyst	Vessel closure or hemorrhage
6.	Diffuse cerebral disease	Degeneration, infection, sclerosis
7.	Diffuse cerebral vascular disease	Arteriosclerosis, syphilis, etc.
8.	Miscellaneous	Congenital lesions, etc.
B.	WITHOUT DEMONSTRABLE CEREBRAL LESIONS	
1.	Cryptogenic (idiopathic, familial)	Abnormal cerebral physiology
2.	Toxic and febrile	Extracerebral causes
3.	Hypoglycemic	Extracerebral causes
4.	Miscellaneous (angioneurotic, circulatory arrest, etc.)	

analyzed 703 verified cases of expanding intracranial lesions in relation to seizures, and their conclusions may be synopsized as follows. There were 149 infratentorial expanding lesions none of which produced epileptic seizures. Seizures in frontal, parietal and temporal lobe lesions were almost twice as common as in occipital lobe lesions. Lesions of the pituitary, thalamus, and basal ganglia produced seizures in only 8 per cent of cases. In a general way seizures become more common as the fissure of Rolando is approached. In a group of 230 verified gliomata occurring above the tentorium, the lowest incidence of seizures was among the most malignant lesions (glioblastoma multiforme, 37 per cent) and the highest incidence among the most slowly growing (oligodendroglioma, 92 per cent). Meningeal fibroblastomata produced seizures in 67 per cent of the cases studied. In the presence of a subdural hematoma the occurrence of seizures probably signifies associated brain injury. In brain abscess, seizures occurred early in the course of the disease in 50 per cent of patients but usually soon disappeared. Months or years later, recurring epileptic attacks might appear due to the cicatrix that had resulted from the abscess. Finally, it was shown that the epileptogenic focus lies in the transition zone between tumor and normal brain, not in the tumor itself and not in the normal brain at a distance from the tumor. The nerve cells in this transition zone are still viable but, because they are in an abnormal environment, they act in an abnormal manner.

ATROPHIC LESIONS

Similar analyses of contracting intracranial lesions are few. Foerster and Penfield (4) have reported on cases of traumatic epilepsy. Penfield and Keith (10) published a study of eight cases of focal epilepsy due to lesions of birth and infancy, and Ford (5) reported eight somewhat similar cases. Penfield and Erickson (7) analyzed a ten-year series of atrophic epileptogenic lesions from the standpoint of results of radical treatment. Childe and Penfield (2) have recently discussed the role of x-ray in the study of local atrophic lesions of the brain.

Procedure: The present investigation has been undertaken to correlate, if possible, the various types of atrophic lesions of the brain with the radiological changes that they may produce. Basic studies have been carried out by Dyke, Davidoff and Masson (3) and by Robertson and Childe (12).

The patients forming the group to be investigated were all operated upon by Dr. Wilder Penfield or Dr. Theodore Erickson between Jan. 1, 1937, and Dec. 31, 1946, a period of ten years. A pathologic diagnosis has been made from excised brain and meninges. A preoperative diagnosis of focal cerebral seizures had been made on the basis of history, physical signs, electroencephalographic examination, and radiological examination with both plain skull films and pneumo-encephalography. In many cases a seizure had been produced and recorded before operation. Frequently the preoperative diagnosis was confirmed by the production of a typical seizure on electrical stimulation of an abnormal gyrus

at operation. All patients who could possibly co-operate were operated upon under local anesthesia, so that electrical stimulation of the cortex could be carried out and electro-corticograms obtained. For the purposes of this study all patients with expanding intracranial lesions were discarded. In some cases the radiographic examinations were done elsewhere and the films are not now available. These are not included. We are thus left with a group of 160 patients.

Films of the skull without contrast media were obtained, as well as encephalograms. The plain skull films consisted of stereoscopic anteroposterior films in Ruggles' projection, stereoscopic lateral films of the abnormal side, and a single postero-anterior film in Caldwell's projection. It was considered essential that there be no rotation of the head when the frontal films were made. Even the smallest amount of rotation produced apparent smallness and flatness of the side of the skull toward which the face deviated, with apparent increase in thickness of the temporal and parietal squama on that side. The convolutional markings on the petrous ridge of that side would seem fewer and flatter, while on the other petrous process they would appear more prominent. Rotation might also cause apparent slight displacement of a calcified pineal gland to one side, though this apparent displacement is less than is usually realized. The anteroposterior films were made with a longitudinal tube shift, never a transverse shift, as a transverse shift always produced some apparent asymmetry of the skull.

One of the frontal films was traced on tracing paper, and the tracing of the skull was folded along the mid-sagittal plane, which was marked by joining the center of the groove for the superior sagittal sinus with the middle of the dorsum sellae. These two points are approximately on the same coronal plane if they are marked on the Ruggles' projection. If there was no groove for the superior sagittal sinus, the sagittal suture was used, but it was not quite as accurate a marker of the mid-line of the brain. It the dorsum was invisible or deformed, the crista galla was chosen as the lower end of the line. When the folded tracing was held before a light, any asymmetry of the skull was easily seen.

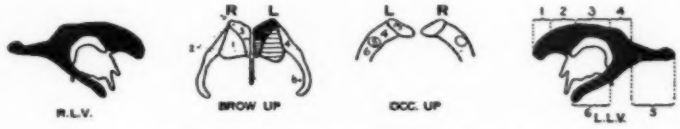


Fig. 1. Normal ventricular outlines.

An average encephalographic study consisted of six stereoscopic pairs of films made in the following successive positions, brow-up anteroposterior and lateral, brow-down postero-anterior and lateral, stereoscopic lateral with the affected side uppermost, and finally stereoscopic lateral with the unaffected side uppermost. In describing the ventricular deformities the nomenclature of Torkildsen and Penfield (13) was used (Fig. 1).

Radiological Findings: Reduction in volume of one lateral chamber of the skull was probably the most important finding on the plain films. It was best shown by the tracing. When the tracing showed asymmetry, the parietal and temporal squama were usually thickest on the small side (Fig. 2). Occasionally they were thin on the small side, and in such cases an underlying collection of fluid in the brain or in the subarachnoid or subdural spaces (Fig. 3) could be postulated. Enlargement of the frontal sinus on the small side was often present, but frontal sinus asymmetry was so common that only when it occurred with other evidence of hemiatrophy of the brain could it be considered significant. Asymmetrical development of mastoid cells in the squamous parts of the

Fig. 2. Examples of cranial hemiatrophy.

A. Case A. J., age 13 years; history of birth injury. Note the small size of the right hemicranium, with increased thickness, increase in size of the right frontal sinus, elevation and smoothness of the right petrous ridge. At operation a large area of brain destruction was found above the posterior half of the sylvian fissure.

B. Case D. M., age 2 1/2 years; history of birth injury. Note the smallness of the left hemicranium, with increased thickness of the bones. There is increased pneumatization of the left petrous process. The left tegmen tympani is higher than the right. The patient was not operated upon because of the age, and because of evidence of widespread left hemispheral damage.

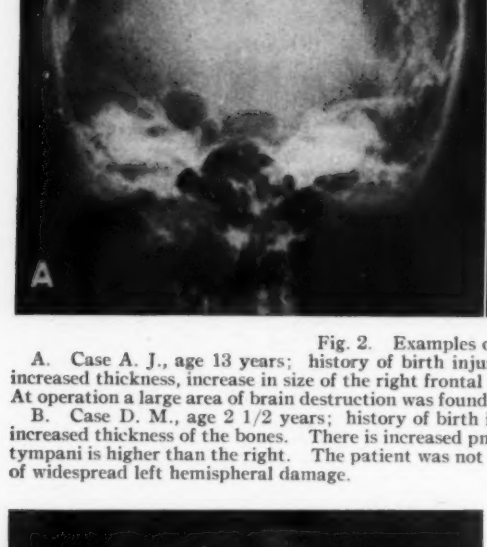


Fig. 3. Case G. L., age 4 1/2 years. The left parietal bone and the left temporal squama are thin. There are localized thinning and bulging just above the center of the left parietal bone. A large subdural cyst, probably the end-result of a subdural hematoma occurring at birth, was discovered.

temporal bones was evidence of asymmetry of the cerebral hemispheres, as were elevation and smoothness of one petrous ridge. This latter might be very noticeable but could be as slight as elevation of the tegmen tympani alone. An occasional finding was deepening of the anterior part of the floor of the middle fossa. Such deepening, if marked, could be noticed in the stereoscopic lateral films. If slight, it was shown only on the anteroposterior films by very slight enlargement of the V-shaped shadow of the antero-inferior portion of the greater wing of the sphenoid bone projected below the base of the posterior fossa. Displacement of the groove of the superior longitudinal sinus to one side of the sagittal suture and elevation of one orbit were less common signs of cerebral asymmetry.

Lesions of the brain occurring within the first two years of life, producing a difference in volume between the two cerebral hemispheres, will cause asymmetrical growth of

the two sides of the skull, because at this time the brain is growing at the maximum rate. Similar lesions occurring between the ages of two years and puberty, when growth is proceeding more slowly, may produce asymmetrical head growth if they are of gross proportions. Lesions occurring after puberty, at which time growth of the brain is fairly complete, will cause no asymmetry of the skull. Unfortunately the degree of cranial asymmetry cannot be correlated with the extent of brain injury. Equal degrees of asymmetry may follow cerebral artery occlusion in one patient and focal compression of two or three gyri in another. The great local ventricular enlargement that occurs in a short time in the first case will allow equal distribution of intraventricular pressure in all directions and apparently compensate for most, but not all, of the destroyed brain. In the second case, only minor local ventricular enlargement takes place, as the abnormal gyri do not disappear completely and as the surrounding gyri grow over the area of microgyria.

The second important finding in these cases was evidence of previous trauma. Fractures that were depressed or in which fragments were separated could be detected years later. Linear fractures, especially in the very young, usually healed completely. Occasionally a row of pits and stalactites along a dural defect would outline an old healed fracture. Quite often an operative defect would be seen. It was interesting to note how often the operative defect and the epileptogenic focus coincided, probably because brain damage beneath the fragment that had had to be elevated produced an area of focal atrophy.

Thirdly, it is important to note any displacement of a calcified pineal, calcified falx, or calcified choroid plexus. In atrophic cerebral lesions these structures are, of course, displaced toward the lesion if it be of any size.

Abnormal intracranial calcification was not common in these cases except for two special groups. In one small group of cases calcification occurred in a very old sub-

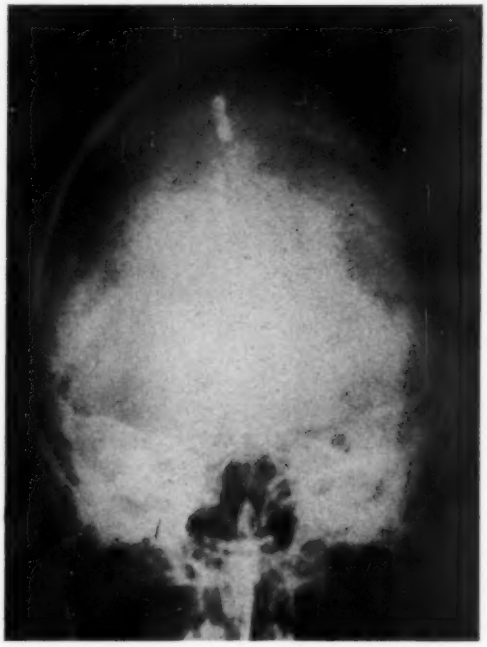


Fig. 4. Case B. P., age 31 years; history of birth trauma with evacuation of a left subdural hematoma at that time. The left hemicranium is slightly smaller than the right; yet the bones on the left are thinner than on the right. There is calcium close to the inner table of the left parietal bone just above its center. The left frontal sinus is enlarged, the left petrous ridge is slightly smooth and elevated, and there are a few more mastoid cells on the left than on the right. At operation there was great thickening and calcification of the dura but no subarachnoid adhesions. The postcentral gyrus and the gyrus posterior to it were atrophic.

dural hematoma (Fig. 4). In the other group a peculiar lesion, best called hemangioma calcificans (11), was found in the temporal lobe. In the latter instance, the calcification occurred in two different patterns of distribution, although histologically it was difficult to determine a sharp distinction. In one type there were numerous faint granules of calcium, 1 to 3 mm. in diameter, scattered through a volume of 4 or 5 c.c. (Fig. 5). In the other type there was a raspberry- or mulberry-shaped, fairly homogeneous, dense calcified mass approximately 1 c.c. in volume (Fig. 6).

The most accurate estimation of atrophy or hypoplasia of the brain was made from the pneumogram. In most cases the dis-

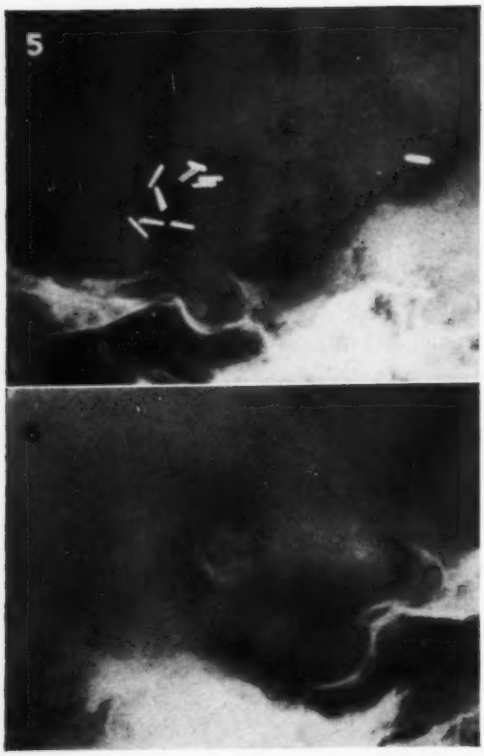


Fig. 5. Case J. S., age 24 years; hemangioma calcificans. Note scattered small flecks of calcium visible through the defect of a previous operation.

Fig. 6. Case P. W., age 33 years; hemangioma calcificans. Note raspberry-shaped mass of calcium in the left temporal lobe.

tance between the ventricular wall and the nearest point of the skull gives an accurate indication of the amount of brain tissue between the two points. When cerebral atrophy was shown, it was not possible to say whether it was gray matter or white matter that had atrophied. In a general way, if ventricular dilatation was generalized, atrophy of white matter was the more likely, while localized ventricular dilatation denoted atrophy of both white and gray matter. Pooling of oxygen in a local area of the subarachnoid space also usually denoted atrophy of both gray and white matter.

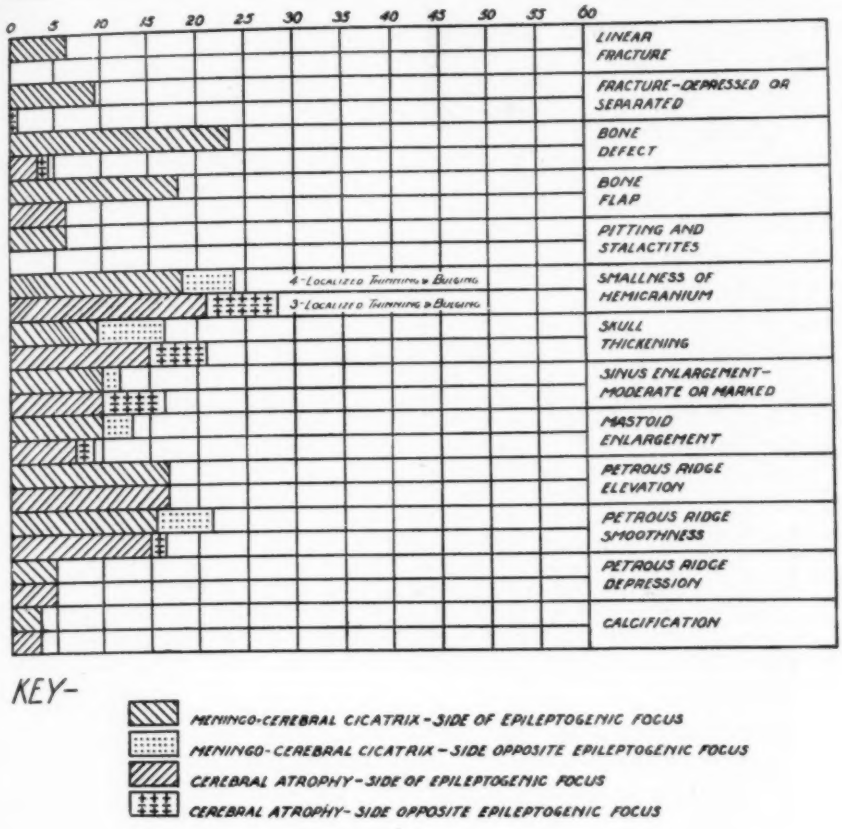
When oxygen entered cysts in the brain or in the subarachnoid space, it was possible to estimate the amount of atrophy with fair accuracy from the thickness of brain between the ventricle and the cyst. Absolute accuracy was not possible, since closed cysts, when present, hindered ventricular dilatation and reduced the shift of the septum pellucidum toward the side of the lesion (12). However, not one case presenting a cyst in the brain was encountered in which some indication of a local lesion was not seen. There was asymmetry of the occipital horns in nearly every instance, but usually the best developed or largest occipital horn was in the dominant cerebral hemisphere. When the largest occipital horn was in the non-dominant hemisphere, there was, with but one exception, an atrophic lesion in the occipital lobe. A study of occipital horn asymmetry in non-epileptic patients is being undertaken in an attempt to confirm our impression that it has some functional significance.

In comparing the lateral ventricles for size and shape, it was necessary to choose perfectly centered films. In measuring septum pellucidum displacement, it was often better to use the falx as the central point rather than the middle of the skull, especially in asymmetrical skulls. If the head was slightly rotated, producing a slight apparent shift of the anterior part of the septum pellucidum, this could usually be corrected by taking measurements from the inner table of the frontal bone rather than from the parietal bones. Slight rotation will also produce apparent enlargement of the anterior horn on the side to which the face deviates.

Small differences in size of the temporal horn shadows had to be interpreted with caution. In normal-sized ventricles, the supracornual cleft (1) is all that is visible, and the width of this shadow varies slightly, depending on the obliquity of the central ray. In the temporal horns that were moderately or greatly dilated, minor differences in size were more significant, as in such ventricles the supracornual cleft had been obliterated.

Meningo-cerebral Cicatrix: Seventy-four cases of meningo-cerebral cicatrix were encountered, 55 in males and 19 in females.

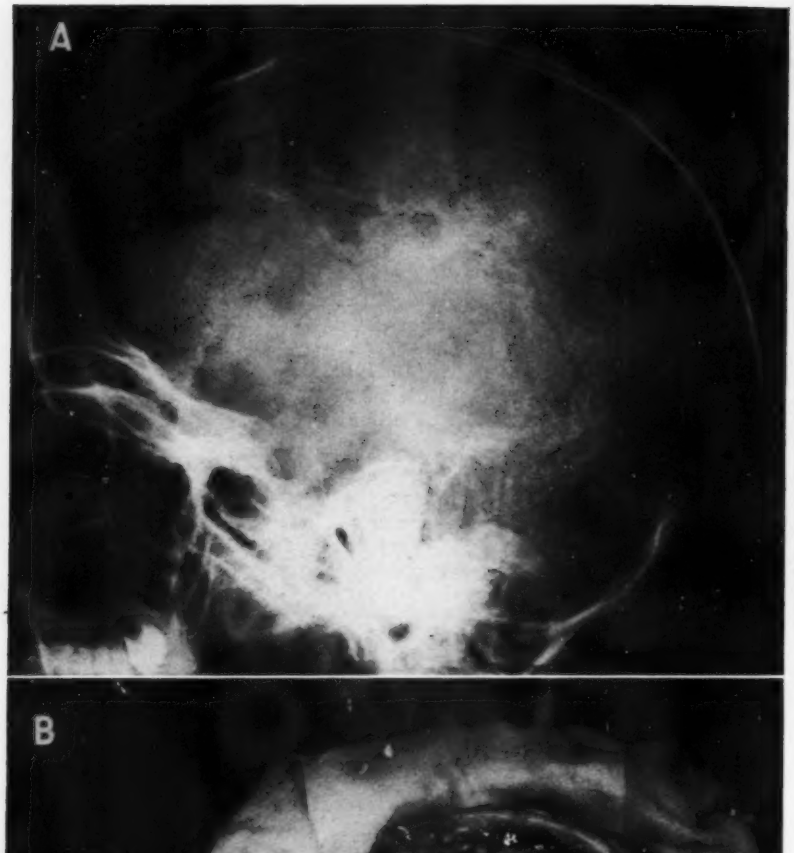
TABLE III: COMPARATIVE RESULTS OF X-RAY STUDY WITHOUT CONTRAST MEDIA



The preponderance of males seemed to be due to two factors: first, boys and men are more exposed to head trauma; second, epilepsy is considered by some people to be a greater economic and social handicap to males than to females, and more males are therefore presented for surgical treatment. The average age was 22.4 years at the time of operation. Many of these patients had had seizures for years, and 18 had had previous operations elsewhere for epilepsy.

Adhesions between the dura and arachnoid may result from the presence of blood in the subdural space, but these adhesions are not dense and they do not contain visible blood vessels. Meningitis may cause similar adhesions. Such adhesions alone probably never cause epilepsy.

Trauma may damage the brain, the dura, or the skull, singly or in combination. If dura and brain are damaged at the same point, a meningo-cerebral cicatrix will form. In a meningo-cerebral cicatrix, however, the subdural adhesions are thick and tough and contain new-formed blood vessels. The scar penetrates the brain, often reaching the wall of the ventricle. The scar tissue contains no nerve cells and therefore does not of itself cause seizures. It is the nerve cells in the intermediate zone between the scar and normal brain that act in an abnormal manner to produce the seizure. An abnormal arrangement of the blood vessels in this intermediate zone has been demonstrated (9) and is possibly responsible for the altered environment of



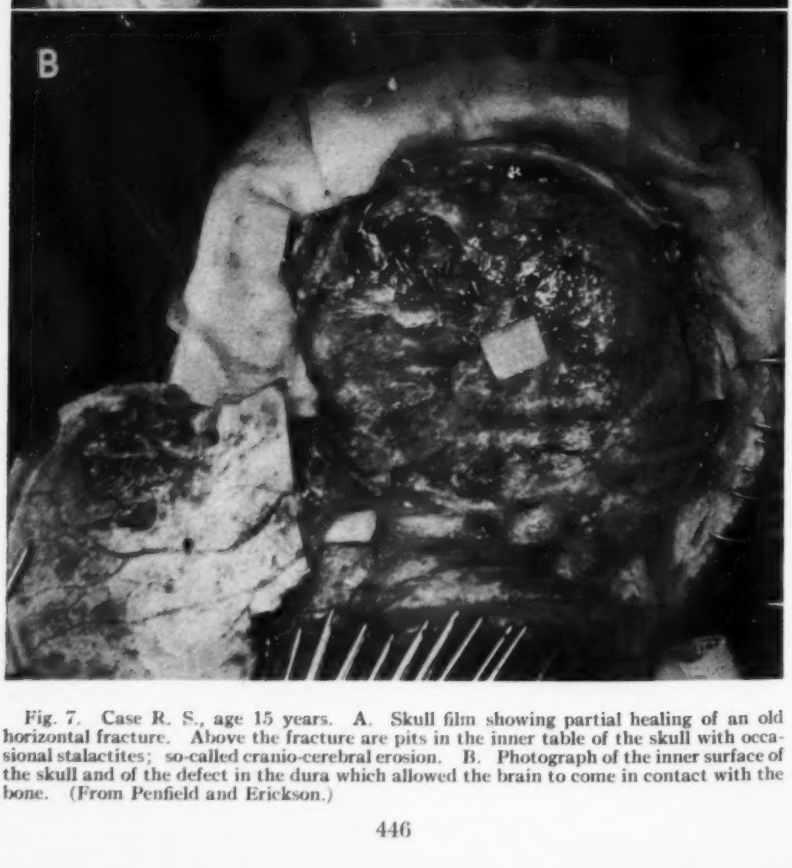


Fig. 7. Case R. S., age 15 years. A. Skull film showing partial healing of an old horizontal fracture. Above the fracture are pits in the inner table of the skull with occasional stalactites; so-called cranio-cerebral erosion. B. Photograph of the inner surface of the skull and of the defect in the dura which allowed the brain to come in contact with the bone. (From Penfield and Erickson.)

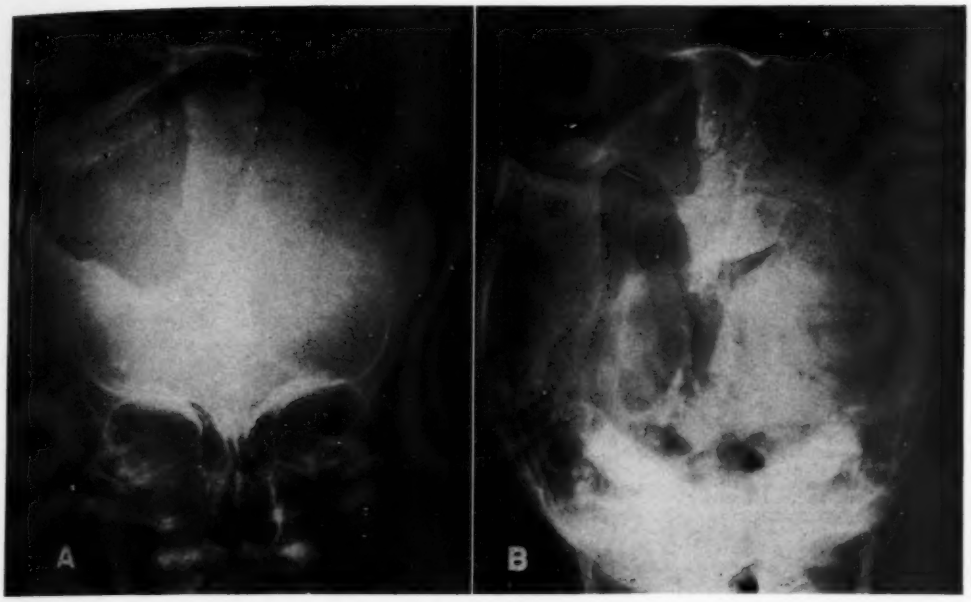


Fig. 8. Case M. G., age 4 1/2 years; skull fracture at the age of six months with subsequent increase in separation of the edges of the fracture.

A. Skull film showing enlargement of right hemicranium, slight elevation of the right petrous ridge, and displacement of the groove for the superior longitudinal sinus to the left. There had been no previous operation.

B. Pneumogram showing focal dilatation of portions 4 and 5, with wandering of the ventricular roof toward the bone defect. There is a cyst in the brain lying beneath the defect and communicating with the ventricle through a small opening.

the nerve cells here. These nerve cells can produce abnormal potentials and by electrical methods may be recognized and localized. If a defect of the dura is present, through which brain (perhaps covered by pia) contacts the bone, the cortex of the inner table of the skull may become eroded in a characteristic manner (Fig. 7). Multiple small pits in the bone are formed, as well as small stalactites. There is often a meningo-cerebral cicatrix at the edge of the defect in the dura.

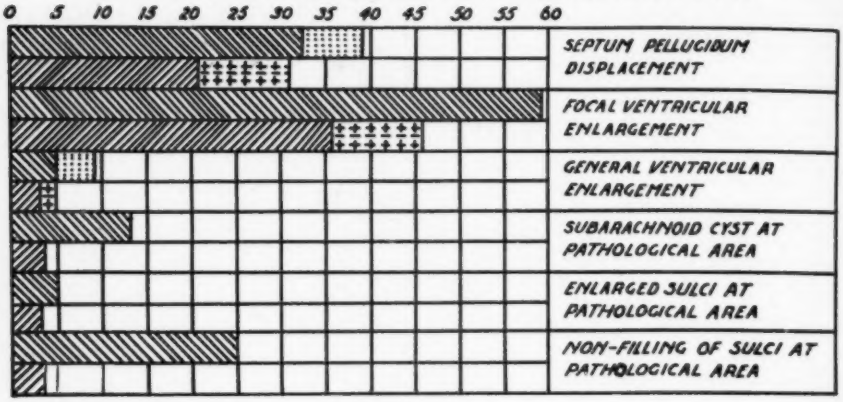
In children, after a "bursting" type of fracture, a linear defect in the dura may persist beneath a linear but separated fracture of the vault (Fig. 8). If the child lives and the dural defect is not repaired, the pressure of the growing brain may lever the fracture edges apart until finally a large oval defect with bevelled edges is produced. A meningo-cerebral scar is usually found at the edge of such a defect.

"Wandering" is a term we use to describe the movement of the wall of the ventricle toward an atrophic lesion that is in addition to or in excess of the movement due to shift of the septum pellucidum and dilatation of the ventricle. It is most often encountered in meningo-cerebral cicatrix and is seen in its most advanced form beneath skull defects, especially the type just described.

Of the 74 patients with meningo-cerebral cicatrix, 18 had had previous exploratory craniotomy. The tracing of the skull could not be accurately made in these patients. They appear in Table III in the column labeled "bone flap." Of the 56 patients who had had no operation for epilepsy, 37 (66 per cent) had a localized bony abnormality that not only disclosed the side that the cicatrix was on but afforded its accurate localization. The 37 cases showed 6 linear fractures, 9 depressed or separated fractures, 23 localized bone defects, 4 local areas of thinning with outward bulging of the bone, and 6 areas of pitting of the inner table with stalactite

TABLE IV

COMPARATIVE RESULTS OF PNEUMOGRAPHY



formation. In some cases two or even three different bony lesions were present in one area. The 23 local bone defects resulted from either previous drainage of a brain abscess or elevation of a depressed fracture with or without débridement of the brain. In the remaining 19 cases, the tracing of the skull showed smallness of the affected side of the skull in 9 and no asymmetry in 6; in 4 the opposite side of the skull was small.

There was slight enlargement of the frontal sinus on the side of the lesion in 15 cases and moderate enlargement in 10. Enlargement of the frontal sinus on the side opposite the lesion was present to a mild degree in 12 cases; to a moderate degree in only 2.

Overdevelopment of mastoid cells in the squama of the temporal bone was present on the side of the lesion in 10 cases and on the opposite side in 3. Elevation of the homolateral petrous process occurred in 17 cases, and the petrous ridge was smooth in 16. In 5 cases there were elevation and smoothness of the petrous ridge on the side opposite the epileptogenic focus.

Pathological intracranial calcification was present in 3 patients. In 2, calcified subdural hematomata were present. In the other there was a raspberry-sized area of granular calcification beneath a meningo-cerebral cicatrix; no reason for this calcification could be found except for the presence of the cicatrix.

The pneumographic findings in the two largest groups are synopsized in Table IV. In the 74 cases of meningo-cerebral cicatrix the lateral ventricles did not fill with oxygen in 3. In 3 patients the lateral ventricles were equal in size and shape, and in 5 there was slight or moderate dilatation of the whole ipsilateral ventricle. In 2 of the latter cases there were cysts beneath the meningo-cerebral cicatrix preventing any localized ventricular dilatation. In 59 patients there was focal enlargement of the ipsilateral ventricle in the area of the cicatrix. Only 4 patients had enlargement of the opposite ventricle, and in each case

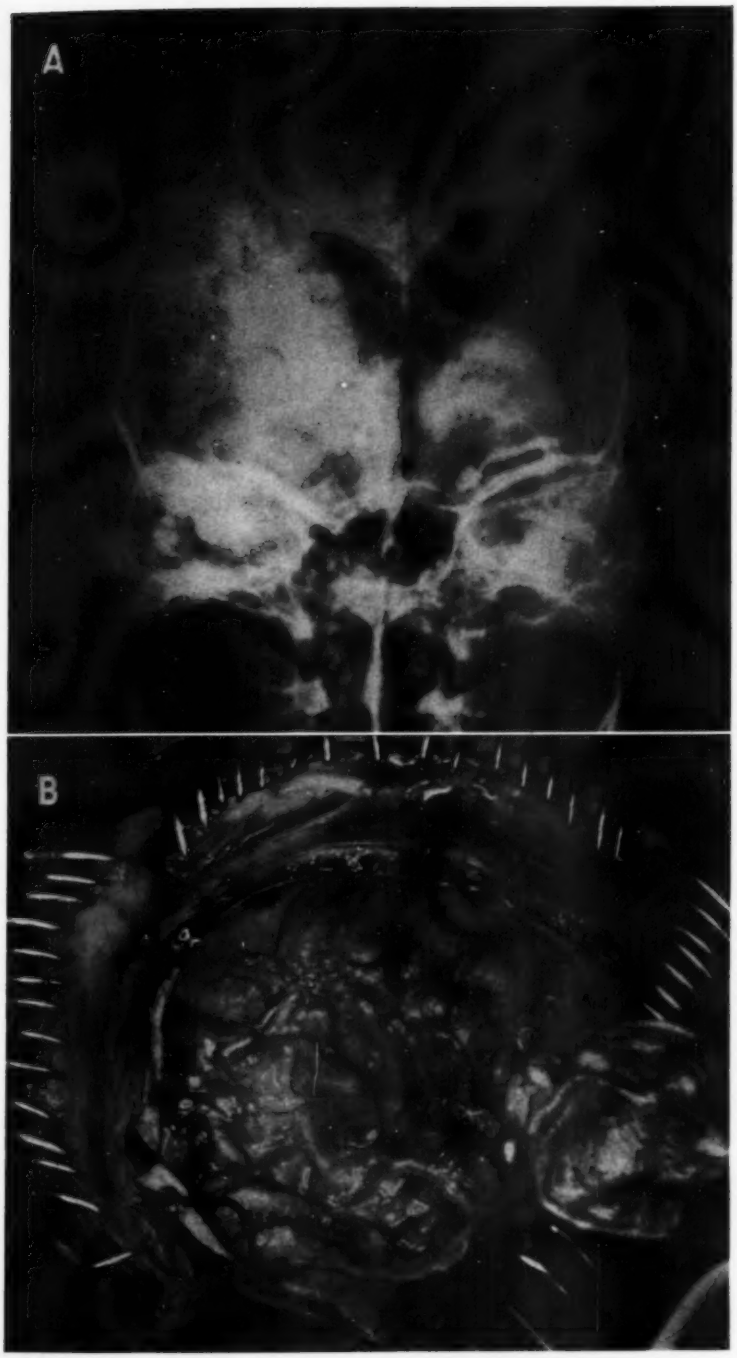


Fig. 9. Case A. M. A. Brow-down film showing gross dilatation of portion 4 on the left. The septum pellucidum is displaced slightly to the left. Note the smallness and thickness of the left side of the vault with slight depression and smoothness of the left petrous ridge. B. Operative exposure. The pre-central and post-central gyri with the first and second temporal convolutions have been destroyed and the wall of the ventricle presents on the surface. The middle cerebral artery branches are absent. (From Penfield and Erickson.)

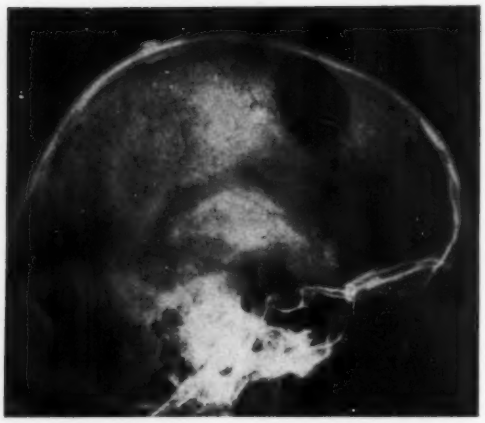


Fig. 10. Case M. S. Pneumogram showing oxygen filling a cup-like atrophic area in, and anterior to, the precentral gyrus.

this enlargement was generalized, not localized. Two of these 4 had had exploratory operations, and after operation the bone flap had become displaced inward. This was considered to be the cause of the relative smallness of the ipsilateral ventricle as well as of the displacement of the septum pellucidum away from the epileptogenic lesion.

Of the 71 patients in whom the septum pellucidum was demonstrated, 33 showed displacement toward the epileptogenic focus. The average of all the displacements was 3.7 mm. In 6 the septum was displaced to the contralateral side, the average displacement being 2.2 mm. In 2 this was due to old subdural hematomata, and 2 had depressed bone flaps; no explanation for the contralateral displacement was discovered in the remaining 2.

Thirteen of the meningo-cerebral cicatrix patients showed oxygen-filled subarachnoid cysts at the scar, and 5 showed definitely enlarged sulci, the sulci at the same area on the opposite hemisphere being filled with oxygen and useful for comparison. In 25 other cases in which there was visualization of the subarachnoid spaces over both hemispheres, there was scant or poor filling of the sulci at the scar. This is of doubtful significance, as all but 3 of the 25 had a bone flap or a bone defect in the scar area.

Simple Atrophic Lesions: Under the heading "simple atrophic lesions" will be discussed cerebral cicatrix, local cerebral atrophy, local microgyria, and brain cyst. The word "simple" implies that only one structure is involved in the lesion, the brain, in contrast to the involvement of both brain and meninges in meningo-cerebral cicatrix. Sixty-two cases of simple atrophic lesion were found, 42 in males and 20 in females.

Arterial occlusion may result in the complete disappearance of brain tissue in a localized area. The destroyed area is replaced by a cyst or obliterated by local expansion of the ventricle (Fig. 9). If seizures follow the occlusion, the focus will be in an atrophied convolution at the edge of the area of destruction. Thombosis of a cortical vein may result in focal atrophy of a portion of the cerebral cortex and an epileptogenic focus may develop at its periphery, also.

In its early stages, a cerebral hemorrhage manifests itself as an acute space-occupying lesion, occasionally with the complication of bleeding into the ventricles or subarachnoid space. If the patient survives, a closed cyst forms, replacing the destroyed brain. If the hemorrhage ruptures into the ventricle or subarachnoid space, a communicating cyst, often spoken of as a porencephalic cyst, may result. The latter will, of course, be filled with cerebrospinal fluid. Focal epilepsy may develop in either type of case and, as usual, the epileptogenic focus will be found in an abnormal gyrus adjacent to the cyst.

Trauma may damage the brain without fracturing the skull or tearing the dura, by producing a contusion or small subpial hemorrhage of the cortex (Fig. 10). A discrete cup-like area in the cortex will result, which is filled with cerebrospinal fluid and which may be filled with oxygen and visualized on the encephalogram.

It is apparent that plain film study of the skull in the 62 simple atrophic lesions was much less valuable. Only one fracture was seen and it was on the contralateral side of the skull. Bone defects were present in the

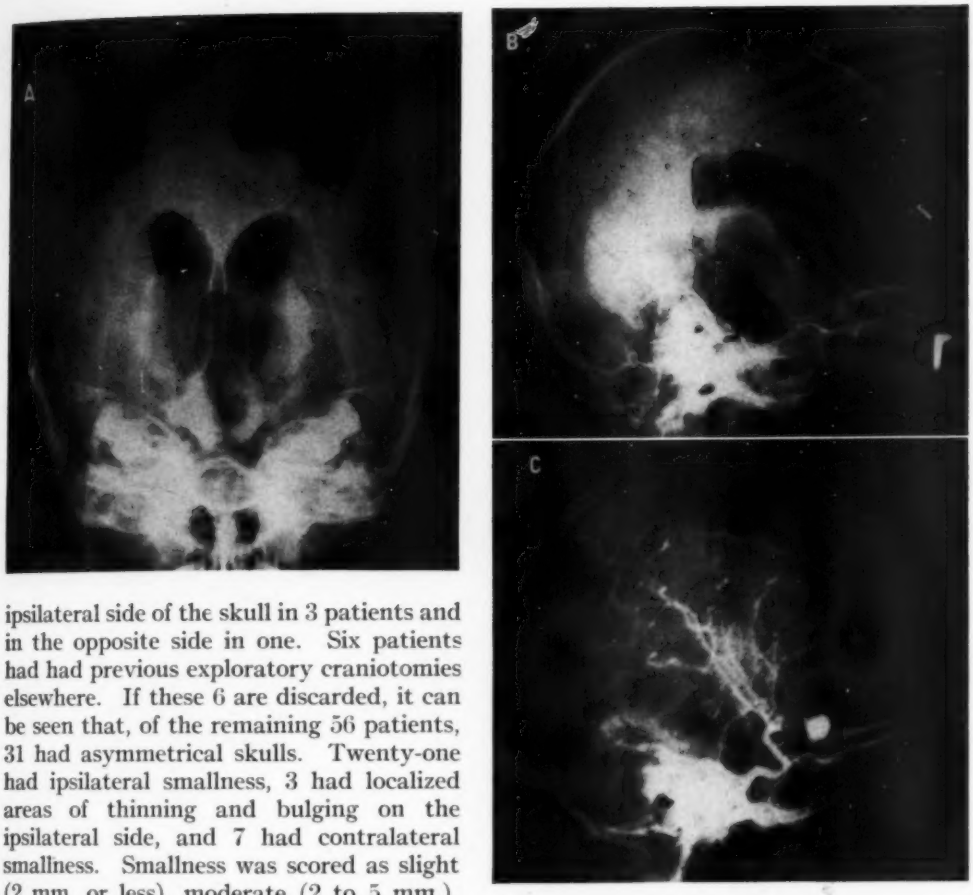


Fig. 11. Case R. O., age 8 years; congenital saccular aneurysm of right anterior cerebral artery which ruptured into the opposite anterior horn. A. Brow-up frontal film showing oxygen filling a small cavity below and medial to the left anterior horn. B. Brow-up lateral film. C. Arteriogram of right carotid artery and its branches. The left carotid arteriogram was normal.

ipsilateral side of the skull in 3 patients and in the opposite side in one. Six patients had had previous exploratory craniotomies elsewhere. If these 6 are discarded, it can be seen that, of the remaining 56 patients, 31 had asymmetrical skulls. Twenty-one had ipsilateral smallness, 3 had localized areas of thinning and bulging on the ipsilateral side, and 7 had contralateral smallness. Smallness was scored as slight (2 mm. or less), moderate (2 to 5 mm.), or marked (over 5 mm.), and the ratio of slight smallness on the ipsilateral side to slight smallness on the opposite side was 10 to 6. The ratio of ipsilateral to contralateral thickening was 15 to 6, approximately the same as the ratio of all cases of ipsilateral smallness to contralateral smallness, which was 21 to 7. Frontal sinus asymmetry was found to be of confirmatory value only. Increased development of mastoid cells in the squama of the temporal bone was not common, occurring but 9 times. In 7 of the 9 it occurred on the side of the atrophic lesion. Not once in the 7 cases was the atrophic lesion found in the temporal lobe.

Asymmetry of the petrous processes was present in 22 of the 62 cases. In 17 patients the petrous process on the side of the epileptogenic lesion was elevated, and in 5 of the 17 the atrophic lesion was in the temporal lobe. In 4 patients the petrous process was depressed, and 2 of these 4 had large cysts in the temporal lobe. In 1 patient all the x-ray findings, including the pneumographic findings, pointed to an atrophic lesion of the opposite frontal lobe, and in this patient the opposite petrous ridge was elevated and smooth. Smoothness of the ipsilateral petrous ridge was present in 15 of the 62 cases, in 6 of which there were temporal lobe atrophic lesions.

The contralateral petrous ridge was smooth in only 2 cases, one of which, mentioned above, gave radiographic and pneumographic evidence of contralateral frontal lobe atrophy.

Fewer of the simple atrophic lesions showed focal enlargement of the ipsilateral ventricle, namely, 36 of the 62. In 10 cases there was contralateral focal ventricular enlargement, in 2 cases contralateral focus. In the other 3, it was impossible to tell from the pneumogram which was the most abnormal side, and in one of these the association of a depressed fracture with a focal ventricular deformity would have placed the lesion on the wrong side except for the clinical and electrographic evidence.

In 21 of the 62 cases, the septum pellucidum was displaced toward the epileptogenic focus. The average displacement was

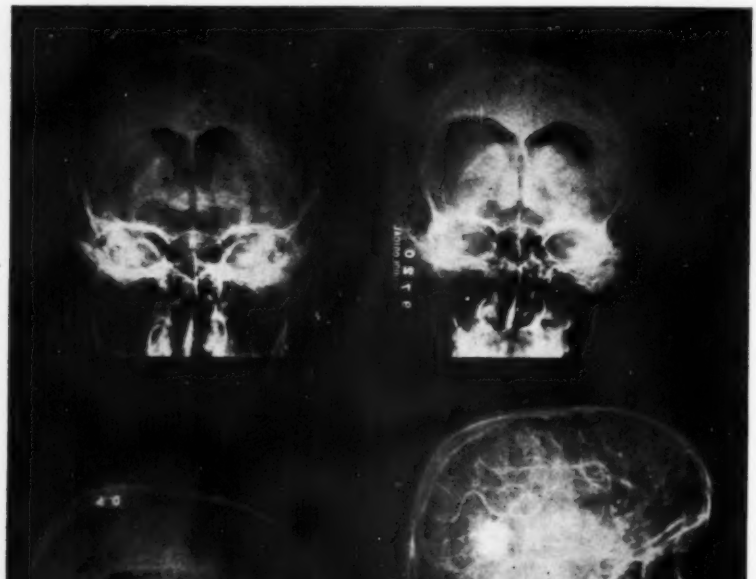


Fig. 12. Case M. M. Arterial angioma involving the angular gyrus on the right side. The focal dilatation of portion 4 of the right lateral ventricle is well shown.

generalized ventricular enlargement, and in 3 cases ipsilateral generalized ventricular enlargement. In 6 cases the lateral ventricles were symmetrical. Five cases showed localized ventricular deformities of both lateral ventricles, and one of these was subjected to operation on both sides. Cysts were found in both cerebral hemispheres. In another, subarachnoid cysts were associated with the local ventricular deformity on the side of the epileptogenic 3.4 mm. In 10 the septum was displaced to the opposite side and in only 3 was the cause of this displacement discovered: 1 had an old subdural hematoma and 2 had depressed bone flaps on the side of the lesion. In 1 of the remaining 7 all evidence pointed to an atrophic lesion on the opposite side.

Deformities of the subarachnoid space were much less common than in the cases with meningo-cerebral cicatrix. In only 3

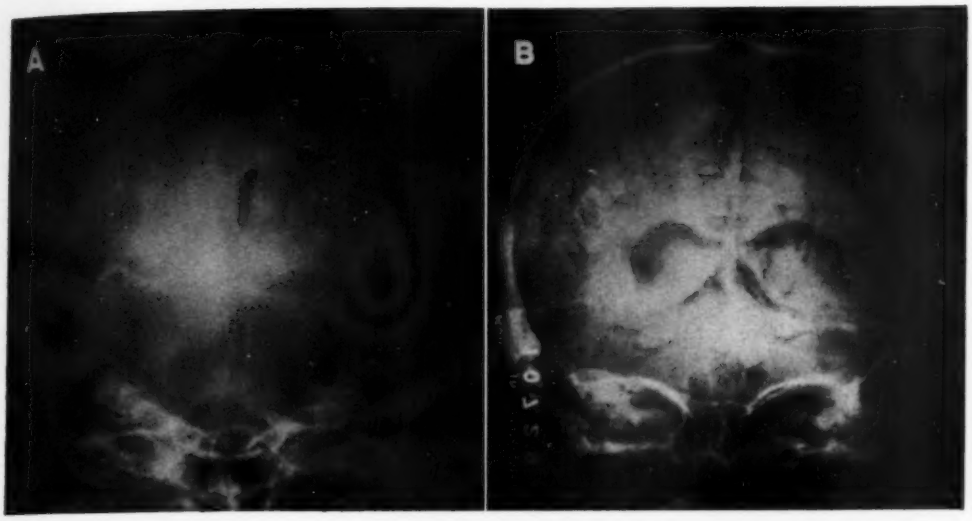


Fig. 13. Case I. I. Calcifying racemose hemangioma in the posterior portion of the right temporal lobe. A. Skull film showing smallness of right hemicranium, thickness of the right parietal and temporal bones, overdevelopment of mastoid cells on the right, elevation and smoothness of the right petrous ridge. B. Pneumogram—brow-down film—showing slight enlargement of portion 4 associated with displacement of portion 4 and the septum pellucidum to the left.

of the 62 did subarachnoid cysts mark the lesion, and in another 3 local dilatation of the subarachnoid sulci was seen. Absence of gas-filled sulci at the pathological area was uncommon, occurring only 4 times, and in 2 of these old bone flaps were present.

Blood-Vessel Anomalies: Blood-vessel anomalies formed the next largest group of lesions in the series. They may produce brain atrophy by three mechanisms. First, rupture of a vessel will produce an area of brain destruction directly (Fig. 11). Second, there may be direct pressure of the vessels on the surrounding brain (Fig. 12). Third, there may be closure of vessels in the adjacent brain. There is often evidence of some expansion as well as of local atrophy (Fig. 13). Occasionally the presenting symptom is subarachnoid or intracerebral hemorrhage. Four of the lesions were of the peculiar type described as hemangioma calcificans (11). In none of the 4 was there cranial asymmetry; 3 showed a calcified area in one temporal lobe. In the case in which no calcium was visible, the lesion was also in the temporal lobe. The other 5 vascular abnormalities were described by the pathologist as follows: hemangioma, 2 cases; racemose hemangioma, 1 case; arteriovenous hemangioma, 2 cases. Only one of these was calcified. One had definite smallness of the hemicranium (Fig. 13).

In the 9 patients with vascular abnormalities, the septum pellucidum was displaced away from the lesion in 2 cases and toward the lesion in 5 cases. The 2 with contralateral septum pellucidum displacement both showed focal ventricular dilatation adjacent to the lesion. Of the 5 with ipsilateral septum pellucidum displacement, there were 2 with focal dilatation and 2 with generalized dilatation of the ventricle on the side of the lesion. The other patient showed slight generalized smallness of the ventricle on the side of the lesion. In 2 of the 9 cases the ventricles were of equal size, without displacement of the septum pellucidum.

Miscellaneous Cases: In 5 cases operation did not disclose a lesion of the brain but did disclose adhesions in the subdural space or in the subdural and subarachnoid spaces. None of these cases presented cranial asymmetry, fracture, or bone de-

fect. In 2 cases the lateral ventricles were symmetrical and equal in size, but in one of these a small subarachnoid cyst was demonstrated just above the area where filmy subdural adhesions were found at operation. In 3 there was localized dilatation of one lateral ventricle, but in only 1 case was it beneath the adhesions.

In 7 cases no lesion of any kind was found at operation. In 2 there was slight but definite asymmetry of the skull, and in both of these there was also ventricular asymmetry to strengthen the suspicion of hemiatrophy or hypoplasia of one cerebral hemisphere. In the others no definite abnormality was shown in the skull films or in the pneumogram.

The remaining 3 cases do not fit into any of the above groups. One was finally classified pathologically as old inflammatory lesion or tumor of the left insula. One was a cuff of bone around a cortical vein, the significance of which is unknown. The final case presented an old calcified subdural hematoma, but no lesion of the underlying brain could be found at operation.

DISCUSSION

The results of plain film examination of the skull in the patients with meningo-cerebral cicatrix are impressive. However, only patients with a very definite diagnosis arrived at by a combination of clinical, electrographic, and radiographic methods were operated upon and then only after medical management had failed. This tends to exclude cases with minimal x-ray findings from the group of patients operated upon. This tendency is even more marked in the case of pneumographic studies. The presence of a localized deformity of the lateral ventricle and/or the subarachnoid space is a great incentive to operate if the atrophic lesion and the clinical localization match. The presence of normal appearing ventricles renders a negative exploration much more likely. It is also possible that the patients responding to medication and hygienic measures have smaller pathological lesions and therefore tend to have more normal appearing skull radiographs and pneumograms. Eley in 1933 published some data on a series of epileptic children that supports this suspicion.

The association of meningo-cerebral cicatrix with fractures, especially depressed or separated fractures, is to be expected, as is also its association with bone defects following elevation of depressed fracture, débridement of the brain, and drainage of brain abscesses.

Smallness of one hemicranium with ipsilateral bone thickening occurs as often in meningo-cerebral cicatrix as in the simple atrophic lesions and is therefore of no differential value. Asymmetry of mastoids, frontal sinuses, and petrous pyramids was also of no differential significance. Localized areas of thinning and bulging of the bone were as common in one group as in the other.

There was no significant difference in the results of pneumography in the two groups, meningo-cerebral cicatrix and simple atrophy. There is an over-all tendency for slight relative increase of positive pneumographic findings in the group with meningo-cerebral cicatrix.

The patients in whom all the x-ray findings pointed to a lesion of the opposite hemisphere probably had an atrophic lesion in that hemisphere that was larger than the epileptogenic lesion. There were 8 such cases among the 160 analyzed, an incidence of 5 per cent. This is a significant percentage and should make one wary of assigning too much localizing value to the x-ray findings alone.

The patients who had skull and/or ventricular abnormalities on both sides form another interesting group. There were 20 of these, an incidence of 12.5 per cent. In 2, depressed bone flaps were obviously the cause. In another, generalized thinning of one side of the skull due to a huge cyst was interpreted as thickening of the opposite side, the cyst preventing any ventricular dilatation on the abnormal side. In 3 patients there seemed to have been a *contrecoup* injury of the brain with

localized dilatations of both ventricles, but all 3 had visible fractures, making it easy to pick out the more significant of the two atrophic areas. One patient had post-traumatic cysts in both cerebral hemispheres. Two adults with post-traumatic seizures had hemiatrophy of the opposite side of the skull and possibly had atrophic lesions on the other side due to lesions of birth or infancy. In 8 cases, I am unable to explain why there were signs pointing to atrophic lesions on both sides, but I suspect there were atrophic lesions in both cerebral hemispheres.

In only 6 of the 136 cases of meningo-cerebral cicatrix and simple atrophic lesion were abnormal intracranial calcifications found, and in 3 of these they were obviously in old subdural hematomata. In 4 of the 9 cases of vascular abnormality pathological intracranial calcification was present. One can say that, if an area of pathological intracerebral calcification is present in a patient with focal epilepsy, the chance of it being in a vascular abnormality is of the order of 15 to 1 if glioma or meningioma can be ruled out.

In 8 of the 136 cases, large cysts within the substance of the brain were found, a group separate and distinct from the patients with a very marked localized dilatation of one lateral ventricle sometimes described as a porencephalic cyst. Four of these cysts communicated with the ventricle by way of a small opening. The presence of the other 4 could not be predicted on x-ray or pneumographic evidence. It was thought that all 8 were the result of old intracerebral hemorrhage. In many others, small cysts in the brain substance or on its surface were encountered at operation. It was impossible to count these accurately, especially the latter group, as the brain fell away after the dura was dissected free, making it difficult to outline them. In addition, small cysts in the brain and/or in the cicatrix were often opened as the dura and scar were dissected away from the surface of the brain.

SUMMARY AND CONCLUSIONS

One hundred and sixty patients with focal epilepsy due to atrophic cerebral and meningo-cerebral lesions have been studied by plain x-ray films of the skull and by encephalography.

The most common atrophic lesion, meningo-cerebral cicatrix, was associated with localized bony abnormalities, namely, old fracture, old bone defect, cranio-cerebral erosion, or localized thinning and bulging of the bone in 66 per cent of cases. Cranial hemiatrophy was present in roughly half the cases. Meningo-cerebral cicatrix was associated with focal ventricular dilatation in 80 per cent of the patients and with demonstrable subarachnoid cysts in 18 per cent. The incidence of localized bone changes is six times greater than in any other type of lesion, a very significant difference. Cranio-cerebral erosion seems to be a specific finding in meningo-cerebral cicatrix.

The simple atrophic lesions, namely, focal microgyria, cerebral cicatrix secondary to arterial or venous occlusion, and brain cysts secondary to cerebral hemorrhage, form the second largest group. In this group, localized bony abnormalities occurred in but 11 per cent. Cranial hemiatrophy was present in roughly half the cases. Focal ventricular dilatation was present in 38 per cent of these patients and subarachnoid cysts were demonstrated in 5 per cent.

The blood-vessel abnormalities form the third largest group of cases, but it is a small group, 9 cases in all. Intracerebral calcification occurred in 44 per cent, an incidence 15 times greater than in any other group. Occasionally in this group, cases will be found in which there are changes suggesting an atrophic lesion associated with changes suggesting a space-occupying lesion. This combination seems to be specific for blood-vessel abnormalities.

The demonstration of a focal atrophic lesion of the brain by no means localized the epileptogenic focus. Eight cases were found in which all the evidence of the skull films and pneumograms indicated an

atrophic lesion on the side opposite that of the epileptogenic focus.

The non-visualization of collections of fluid, such as subarachnoid or intracerebral cysts, was the source of most of the errors in diagnosis.

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DISCUSSION

Bronson Crothers, M.D. (Boston, Mass.): This situation is impossible to discuss on fair terms because Dr. McRae has had the extraordinary opportunity of working consistently with a resolute optimist and a very daring and successful surgeon. There are many daring and successful surgeons who are pessimists so far as most of the focal epilepsies are concerned. For that reason I should think that the discussion must be on the basis of very little optimism and therefore limited experience.

It has seemed to me right along that the problem of epilepsy, of feeblemindedness, and of cerebral paralysis is so desperate that any method is justified if it gives results without too great danger.

One problem has had to be faced by us very definitely. In Boston, as everywhere else, expensive medical care has gone up steadily in cost. At the same time, the facilities of the x-ray department have been restricted to some extent by scarcity of film over a considerable number of years, so that the use of films which are not going to be directly useful has been deprecated all along the line—by the patient who pays the bills, by the radiologist who has other use for his films, and by the hospital administration.

Obviously no complete study can be made without preliminary flat plates, and in this connection I should like to ask Dr. McRae how many times surgical intervention was decided upon without pneumoencephalograms. Also, how many times flat plates settled the problem completely. I think there is no question of the logic of having flat plates. We have used them routinely where we were afraid of pressure.

Pneumoencephalography is a fairly safe procedure. With reasonable precautions the mortality is low, that is, with a staff that is competent to do even a lumbar puncture. No one ought to undertake a lumbar puncture until he understands enough of the signals of pressure to do it in the presence of a tumor, which may give trouble.

The one error that we have all fallen into at one time or another is the assumption that a pneumoencephalogram tells the story for all time. That is, people have become so pessimistic in their attitude toward injury to the nervous system as being irreversible and final, and have become so attached to these measurements of one sort and another, that a single film is assumed to have implications of all kinds as a permanent record.

Now on repeated pneumoencephalography, we have many times found changes in both directions. It would seem, therefore, to be like every other technical procedure, valid at the time it is done and valid for the purposes for which it is adopted, largely to demonstrate change in brain mass, which it shows most distinctly.

I would like to ask Dr. McRae whether he does not believe that uneven pressure is the only factor that will push the whole ventricular system over to one side or the other. Acceptance of that as a working hypothesis will keep one out of any number of troubles. The pull of a scar is valid enough for distortion of a single ventricle but it doesn't seem to me to explain the total shift. The age distribution of these cases has an obvious bearing here; for, of course, the more rapidly the brain is growing, the more completely pressure of growing tissue will throw the ventricular system over to the other side.

Having had the opportunity of reading Dr. McRae's full paper, I am aware that he has answered most of my questions and that this discussion merely amplifies his condensed report.

Donald McRae, M.D. (*closing*): Dr. Crothers has asked how many times diagnosis of focal atrophic lesion was made by the plain film. In 66 per cent of the 72 cases of cerebro-meningeal cicatrix not only could the diagnosis be made but the lesion could be localized. In the third group of cases, the vascular lesion could be localized and a diagnosis made in 4 of the 9, about 45 per cent.

SUMARIO

Epilepsia Focal

A 160 enfermos con epilepsia focal debida a lesiones encefálicas y meningo-encefálicas atróficas se les estudió por medio de películas radiográficas simples del cráneo y por medio de la encefalografía.

La lesión más frecuente, cicatriz meningo-encefálica, se hallaba asociada a anomalías óseas localizadas, a saber, fracturas antiguas, antiguas deformaciones óseas, erosión cráneo-cerebral, o adelgazamiento y abultamiento localizados del hueso en 66 por ciento de los casos. Más o menos en la mitad de los casos existía hemiatrofia craneal. En 80 por ciento la cicatriz meningo-encefálica coexistía con dilatación ventricular focal y en 18 por ciento había quistes subaracnoideos observables. La incidencia de alteraciones óseas localizadas es seis veces mayor que en ninguna otra forma de lesión, lo cual representa una diferencia muy importante. La erosión cráneo-cerebral parece constituir un hallazgo específico en la cicatriz meningo-encefálica.

Los lesiones atróficas simples, o sean, microgiria focal, cicatriz encefálica secundaria a oclusión arterial o venosa y quistes cerebrales secundarios a hemorragia cerebral, forman el segundo grupo en magnitud. En este grupo, sólo se observaron anomalías óseas localizadas en 11 por ciento. Toscamente, en la mitad de los casos había atrofia hemicraneal, en 38 por ciento dilatación focal de los ventrículos y en 5 por ciento quistes subaracnoideos.

Las anomalías vasculares constituyen el tercer grupo de casos, bien pequeño por cierto, pues sólo comprende 9 casos. En 44 por ciento había calcificación intracerebral, o sea una incidencia 15 veces mayor que en ningún otro grupo. De cuando en cuando, encuéntranse casos con alteraciones indicativas de una lesión atrófica vinculada con una patología que sugiere la existencia de una lesión localizada en cierto espacio. Esta combinación parece ser específica de las anomalías vasculares.

El hallazgo de una lesión atrófica focal del cerebro no servió en modo alguno para localizar el foco epileptógeno. Descubriéronse 8 casos en los que todos los datos aportados por las radiografías craneales y las neumografías indicaban una lesión atrófica del lado opuesto al del foco epileptógeno.

La causa de la mayor parte de los errores de diagnóstico radicó en no visualizarse las aglomeraciones de líquido, por ej., en los quistes subaracnoideos o intracerebrales.

Bone Involvement in Malignant Lymphoma[1]

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THE PURPOSE OF this study is to review the problem of involvement of bone by malignant lymphoma, to attempt to determine what influence, if any, such involvement may have on the course of the disease and well-being of the patient, and to try to solve such other problems related to the disease as the extent and nature of the data available will allow. In the Tumor Clinic of the Massachusetts General Hospital, in the ten-year period from January 1936 through December 1945, a clinical diagnosis of lymphoma of one variety or another was made in 402 patients.[2] In 313 of these the diagnosis was proved by histologic examination, either of a specimen secured by biopsy or during a surgical operation, or at autopsy. Discarding 25 cases of mycosis fungoides, there remain 288 histologically proved cases upon which the following review is based.

The determination of involvement of bone was by means of roentgenograms and by postmortem examination. In one case only was bone involvement found postmortem which had not been previously recognized roentgenologically. While it is well known that considerable involvement of bone by tumor is necessary before demonstration by roentgenogram is possible, it would seem that in these cases of malignant lymphoma the disease progressed slowly enough so that the majority of the bone lesions were diagnosed antemortem.

Exclusive of the leukemias and the disease which is termed paragranuloma by Jackson and Parker (5, 6), the classifications adhered to in this community are that of the latter authors and that of Gall and Mallory (3); the two are quite similar save for nomenclature.

Gall and Mallory	Jackson and Parker
Stem-cell lymphoma	Reticulum-cell sarcoma
Clasmatocytic lymphoma	Reticulum-cell sarcoma
Lymphoblastic lymphoma	Lymphosarcoma
Lymphocytic lymphoma	Lymphosarcoma
Hodgkin's lymphoma	Hodgkin's granuloma
Hodgkin's sarcoma	Hodgkin's sarcoma
Follicular lymphoma	Giant follicular lymphoma

For the purpose of this study, and in order that no individual group may be too small, the classification of Jackson and Parker is used.

TABLE I: DISTRIBUTION OF ALL TYPES OF MALIGNANT LYMPHOMA AND OF CASES SHOWING BONE INVOLVEMENT

Type of Lymphoma	A, Total No. Cases	Bone Involvement B, No. Cases	Bone Involvement C, Per Cent of Group
Reticulum-cell sarcoma	58 (20%)	12 (32%)	21
Lymphosarcoma	81 (27%)	10 (26%)	12
Hodgkin's granuloma	86 (30%)	12 (32%)	14
Hodgkin's sarcoma	16 (6%)	1 (2.5%)	6
Giant follicular lymphoma	23 (8%)	0	0
Undetermined	24 (9%)	3 (7.5%)	12
TOTAL	288 (100%)	38 (100%)	

INCIDENCE OF BONE INVOLVEMENT

In Table I, Column A shows the grouping of the 288 cases. Hodgkin's granuloma is the most commonly occurring form of malignant lymphoma, almost one-third of the patients falling into that group; Hodgkin's sarcoma and giant-cell follicular lymphoma are the least common, each accounting for less than 10 per cent of the series.

Of the entire group of 288 patients, 38 or 13 per cent had manifest involvement of bone at the time of the first observation or sometime later in the course of the disease. As seen in Column B (Table I), the in-

[1] From the Department of Radiology and the Tumor Clinic of the Massachusetts General Hospital, Boston 14, Mass. Accepted for publication in July 1947.

[2] A corresponding series for the preceding ten-year period was reported by Dresser and Spencer in 1936 (2).

cidence of discrete bone involvement in each group of patients roughly parallels the frequency of the disease in the group as a whole, with the exception of the giant-follicular type of lymphoma in which the figure is disproportionately low. No instance of bone involvement was found in this group, although others have reported an occasional case, and there are two instances known in this hospital which do not fall within the time period at present under consideration.

As to the chances of a person with any particular type of lymphoma having bone involvement, it is seen (Table I, Column C) that the occurrence in reticulum-cell sarcoma is somewhat disproportionately high—1 in 4.8 patients, compared to 1 in 8 in Hodgkin's granuloma and in lymphosarcoma and 1 in 16 in Hodgkin's sarcoma. It is thus seen that the histology may somewhat influence the occurrence of bony involvement. Recognizing that the data do not account for the diffuse bone marrow disease found only by histologic bone marrow examination or by the presence of myelophthisic anemia, these figures compare quite favorably with those of Gall and Mallory (3).

Of the 38 patients with lymphoma of all types with bone involvement, 15 had solitary lesions, the distribution of which in the skeleton follows fairly closely that of multiple bone lesions (Table II). In all,

TABLE II: DISTRIBUTION OF BONE LESIONS IN THE SKELETON

Bone Involved	Solitary Lesions		Total Lesions	
	No. Cases	Per Cent	No. Cases	Per Cent
Skull	2	12.5	15	13
Spine	4	31	46	41
Pelvis	2	12.5	11	10
Sternum	3	19	3	3
Ribs	1	6	12	10
Extremities	3	19	18	16
Pectoral girdle	...	...	8	7
TOTAL	15	100	113	100

there were 113 separate areas of bone involvement in the patients considered. As has been noted by others (4), the spine is the most frequently affected.

Of the 15 solitary lesions, 5 were reticulum-cell sarcoma, representing the highest relative incidence of solitary lesions; 4 were lymphosarcoma, 4 Hodgkin's granuloma, and 2 were of undetermined classification (Fig. 2). Solitary bone involvement in reticulum-cell sarcoma has been known to occur as the only evidence of tumor and as such it has occasionally been found to be curable. Two patients in this group who had reticulum-cell sarcoma of an extremity have survived for more than ten years after treatment, by x-radiation in one and by amputation in the other.

AGE INCIDENCE

The ages of the 288 patients studied ranged from seven to eighty-three years; the age range for those showing bone involvement was from eleven to seventy-four years (Fig. 1). The incidence of involvement of bone according to decades was found to parallel roughly the age distribution of the group as a whole. Figure 1, however, suggests that there may be a slight tendency to the development of bone lesions in the younger group, the greatest incidence being in patients of the fourth decade, whereas the highest incidence of the disease in the entire group did not occur until the sixth decade. Since the total numbers are small, these indications may not be conclusive, but the inference is that younger patients are more inclined than older ones to have lesions of bone. This may be explained, however, on the basis of greater life expectancy of younger individuals.

SEX INCIDENCE

Of the entire group, 161 patients were male and 127 female, or a ratio of 1.3 to 1. Compared to this, the occurrence of bony involvement was found to be equal in the two sexes, 19 of each, or a ratio of 1 to 1. This relatively higher manifestation of bone lesions in the female need not be significant in a series no larger than that presented here. A similar tendency, however was reported by Craver and Copeland in Hodgkin's granuloma (1).

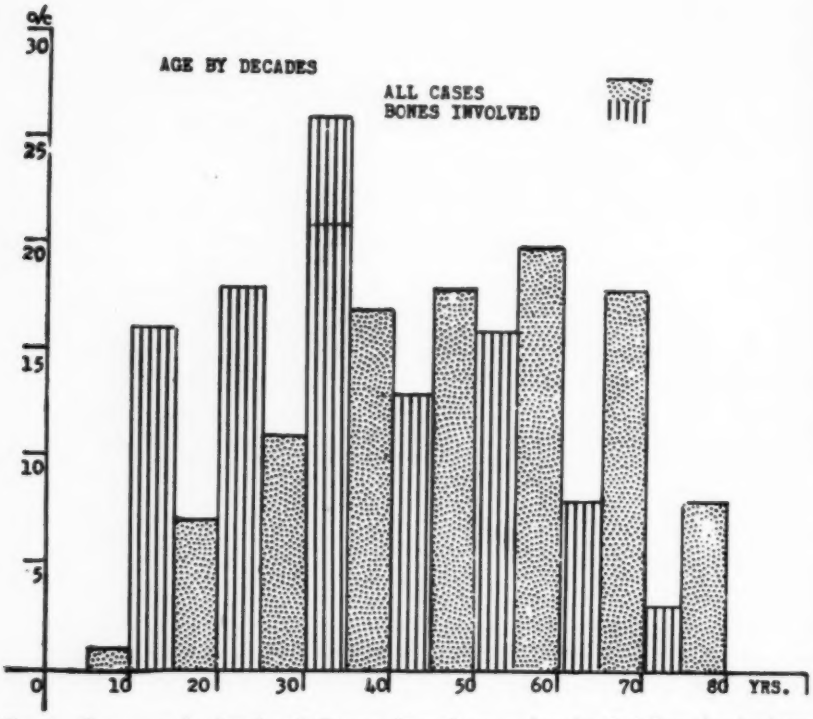

FIG. 1. Occurrence by decades of all cases of lymphoma reviewed and of those showing bony involvement.

EFFECT OF BONE INVOLVEMENT UPON CLINICAL COURSE OF DISEASE

Of all the patients with malignant lymphoma, somewhat more than 10 per cent have been found to show involvement of bone at some time in the course of their disease. It is the rare patient, however, whose attention is first called to the disease by the bone lesion. In the group studied, there was only one such case in addition to the two of primary reticulum-cell sarcoma previously described. In the remainder, symptoms referable to the skeletal system developed at varying times during the course of the disease. Almost without exception bone pain, with or without accompanying palpable tumor, was the clinical finding which brought the involvement to the notice of the patient and of the physician. Rarely was a painless swelling noted or was bony destruction first discovered on routine roentgenograms.

That in malignant lymphoma of any type the course is little influenced by the presence of bony involvement is shown in Figure 2. The average duration of the disease in all the patients seen in the Clinic during the course of observation was slightly over forty months, and the average duration in patients with bone involvement was almost forty-five months. Notable exceptions to this are the two patients with solitary involvement of bone by reticulum-cell sarcoma, both of whom are clinically free of disease ten years after treatment. Patients showing bony involvement may live as long or longer, though perhaps more uncomfortably, than those without such involvement.

As a whole, the time of appearance of bone involvement is somewhat indiscriminate. In reticulum-cell sarcoma, it was close to the end of the course, except in those patients in whom the involvement was early, solitary, and primary, in which event the chances for long-term

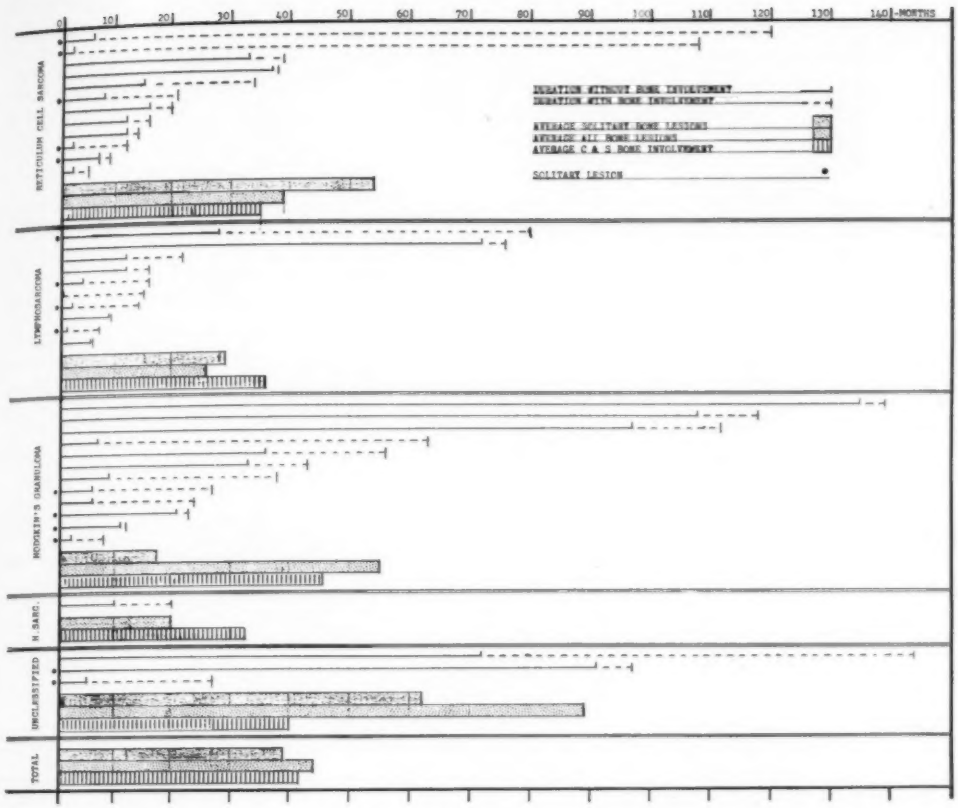

FIG. 2. Individual duration of disease before and after the appearance of bony involvement in the various types of lymphoma, the average duration of the 38 cases showing bony involvement, and the average for the entire 288 cases.

survival after adequate treatment are considerable. In Hodgkin's granuloma, also, bone involvement tends to be a late happening when it develops in those individuals whose span of disease extends beyond the average for the group. Otherwise, this complication seems to be manifest at random in either the early or latter half of the period of the disease and has no great value as a prognostic sign.

TREATMENT

With the exception of solitary osseous involvement by reticulum-cell sarcoma, where the object is to try to cure, the attitude in the treatment of bone lesions has been essentially that entertained in the treatment of malignant lymphoma in general, that is to say, an attempt at palliation, the intent being to relieve symptoms as they appear. It was found that this may be accomplished by amounts of radiation varying from 600 r to 1,500 r. One patient with reticulum-cell sarcoma of a femur (mentioned above), who has survived for ten years without disease, received a total of only 1,200 r, 200-kv. therapy. Usually a somewhat larger dose of x-rays is needed to produce relief from bone pain than is ordinarily necessary to cause regression in an area of soft-tissue involvement. Unless the occurrence of bone involvement was a near terminal event, reactivation of the bone lesion at unpredictable periods of time after treatment was quite the rule, and palliative measures were repeated many times during the course of years.

SUMMARY AND CONCLUSIONS

Of the 288 cases of malignant lymphoma of all varieties seen during the ten-year period under consideration, 13 per cent were found to present involvement of bone. The spine was the most common site. With the exception of solitary reticulum-cell sarcoma of bone, which may be a curable disease, the appearance of bone involvement seems to have no notable effect upon the prospect for survival of an individual beyond that which is well recognized for the various subgroups of the disease. Neither does the time of the appearance of the bone lesion, whether early or late in the course of the disease, affect appreciably the ultimate prognosis, except in widespread reticulum-cell sarcoma, when it tends to occur terminally.

Giant follicular lymphoma was found to involve the skeletal system in a disproportionately low degree; recticulum-cell sarcoma in a relatively high degree.

No significant age or sex predilection for bone involvement in malignant ymphoma was found.

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SUMARIO

Invasión Osea en el Linfoma Maligno

De 188 casos, histológicamente comprobados, de linfoma maligno, observados en la Clínica de Tumores del Hospital General de Massachusetts en el decenio que terminó en diciembre de 1945, en 13 por ciento se encontró el hueso invadido. El raquis fué el asiento más frecuente. Exceptuado el sarcoma reticulocelular del hueso, que puede resultar curable, el aspecto del hueso invadido no parece ejercer mayor efecto sobre las probabilidades de curación de un individuo, aparte de lo que está ya bien reconocido para los varios subgrupos de la enfermedad. Tampoco afecta apreciablemente el pronóstico definitivo la fecha de la aparición de las lesiones óseas, y sea temprana o tardíamente en la evolución de la dolencia, excepción hecha del sarcoma reticulocelular generalizado, en el cual suelen aparecer al final.

Según se observó, el linfoma folicular gigante invade el esqueleto en una proporción por demás pequeña; el sarcoma reticulocelular en una proporción relativamente grande. No se notó ninguna predilección significativa en cuanto a edad o sexo para la invasión ósea en el linfoma maligno.

Tumor Dose in Cancer of the Larynx[1]

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A STUDY OF 113 cases of cancer of the larynx admitted to the Radiotherapy Department of the Presbyterian Hospital, (New York) from April 27, 1928, to Nov. 21 1944, was made with special reference to the tumor doses. In view of the more accurate knowledge recently acquired concerning the cancerocidal dose, it was thought that a considerable variation in dosage might have existed over this sixteen-year period and that the differences might offer some explanation of the vagaries of response to x-ray treatment.

The terms extrinsic and intrinsic as applied to laryngeal lesions were found to be too inclusive for the purposes of this analysis. To avoid any possibility of confusion as to the origin and extent of the disease, a more specific anatomical division was necessary. Lederman (7) suggested an excellent classification of laryngeal carcinomas from a radiotherapeutic point of view, but it was considered too detailed to be of any value in the small number of cases available for this study. The cases were therefore classified as follows:

1. Lesions restricted to the vocal cord (Group 1A).
2. Lesions arising on the cord with extension to other structures within the larynx without involvement of the lymph nodes (Group 1B).
3. Lesions arising on the cord with extension to other structures within the larynx and to the lymph nodes (Group 1C).
4. Lesions exclusive of the cord but limited to a single structure within the larynx (Group 2A).
5. Lesions exclusive of the cord involving two or more structures within the larynx without extension to the lymph nodes (Group 2B).
6. Lesions exclusive of the cord with extension to the lymph nodes (Group 2C).

The selection of cases of carcinoma of the larynx for treatment by irradiation has been discussed in detail by various authors (1, 3, 4, 8–11, 13). The small lesions of the true cord, centrally located, with no impairment of mobility, are equally amenable to laryngofissure or irradiation. Laryngofissure or cordectomy results in a husky, low-pitched voice which may influence the patient in favor of irradiation. Subglottic extensions, with few exceptions, are not cured by x-ray therapy and, unless contraindicated by the patient's general condition or extensive disease, laryngectomy is the treatment of choice.

Lesions of the band respond to x-ray therapy, yet tend to recur. With local disease and no surgical contraindication, laryngectomy is preferable. Lesions of the arytenoid and pyriform sinus are particularly difficult problems because laryngectomy often fails to remove all the disease and response to irradiation is not very satisfactory. A few cases may be salvaged by laryngectomy plus a full postoperative course of irradiation. Epiglottic lesions, particularly non-invasive types, do well with x-ray therapy, and in this instance it is the treatment of choice.

Treatment may be indicated according to the above criteria but often the final decision is made by the patient. Many have not only a deep-seated fear of operation but a dread of being unable to speak. No matter how we strive to prepare the patient for operation, he may refuse and irradiation must be given.

For appraising results, three years was selected as the minimum survival period, on the basis of the statement by Cutler (1) that early carcinomas limited to the vocal cord, treated by adequate x-ray therapy,

[1] Accepted for publication in August 1947.

rarely recur after two years' freedom from disease. It is useful in the others to illustrate how long a patient can survive with disease, a point often overlooked.

All the lesions in this series were squamous-cell epitheliomas. During the work-up, they were classified, where possible, as well, moderately, or poorly differentiated. Analysis of the review, however, seemed to indicate that differentiation did not have as much bearing on the response to irradiation as might have been expected, and this feature has not been included in the tables. This impression is corroborated by Harris and Klemperer (2).

In calculating the dose to the tumor, its depth was considered to be 4 cm. on the affected side and 6 cm. from the opposite side. Over the period of years, the size of the fields and the air dose varied considerably, making a separate calculation necessary in each case in order to obtain accurate figures for the tumor dose.

In treating the cases presented, two lateral fields were used, with the larynx centrally placed, so that it was uniformly irradiated throughout its extent. Fields varied in size from 10 × 10 cm. to 7 cm. in diameter, with only occasional use of a a field 5 × 5 cm. The treatment period ranged from three weeks to sixteen weeks. Early in the series the tendency was to give the treatment in three to four weeks with large fields and high daily dosage, averaging 350 r in air per day. The pendulum then swung in the opposite direction, the treatment period being extended to six to eight weeks with smaller fields (7 cm. in diameter) and a smaller daily dose. The average daily dose now is 125 r in air to each of two fields. When a membrane appears, usually half way through a course of therapy, treatment is interrupted until the membrane begins to subside. The factors are 200 kv., 25 ma., 50 cm. T.S.D., and 1 mm. Cu plus 1.25 mm. Al filter.

Tumor doses delivered by various technics approach the dose that is customary today, approximately 5,000 r. Blady and Chamberlain (3) used a 5 cm. and a 7 cm. depth as the tumor site in calculating the dosage for their cases of cancer of the larynx and quoted tumor doses for fields of various dimensions for both. Their factors were 180 kv. constant potential, 5 ma., 50 cm. T.S.D., with 2 mm. Cu plus 1 mm. Al filter. The daily dose was 125 r in air to each of two fields. The average total dose in air to each area was 3,000 r. With this technic the depth dose at 5 cm. was 3,576 r for a 5.5-cm. cone and 4,680 r for a 10 × 10-cm. field. Occasionally 4,000 or 5,000 r in air was given to each of two fields. For the small field the tumor dose was 4,758 r when 4,000 r was given and 5,960 r when 5,000 r was given. The same proportionate increase to 6,240 and 7,800 r was achieved with a large field. The five-year survival rate for the lesions classified by them as intrinsic was 59 per cent and for the extrinsic lesions 25 per cent.

Howes and Platau (4) suggest that a carcinogenic dose is 4,875 r or higher, given in one cycle. The patients who survived in their series actually received higher tumor doses, 5,000 to 7,800 r, delivered in one cycle of seven weeks. The survival rate was 23.75 per cent, but 4 patients lived less than three years. The series included extensive, inoperable, intrinsic lesions as well as extrinsic lesions.

Cutler's (1) basis for treatment is the use of large daily doses over a comparatively short time, nine to twelve days, and a dose sufficient to produce epithelitis. For advanced extensive lesions eighteen days are required. Radioresistant tumors must have an adequate daily dose as well as an adequate total dose.

Several technics were used by Cutler. With 400 kv., 5 ma., 5 mm. Cu filter, 85 cm. T.S.D., and a field decreased from 30 sq. cm. to 20 sq. cm., 3,600 r on the skin were given in eight days. As the field was decreased, the daily dose was increased. Two treatments were given per day. Twelve days later a second cycle was given to the opposite side, in which the total was 4,000 r and the fields were decreased from 30 sq. cm. to 12 sq. cm. The tumor dose was calculated to be approximately 5,550 r.

TABLE I: CORD LESIONS: SURVIVAL PERIODS
(Figures Are Case Numbers)

Tumor Dose, r	Small Lesions					Extensive Local Lesions					Extensive Lesions with Nodes				
	Under 1 Yr.	1–2 Yr.	2–3 Yr.	3–5 Yr.	5–10 Yr.	Under 1 Yr.	1–2 Yr.	2–3 Yr.	3–5 Yr.	5–10 Yr.	Under 1 Yr.	1–2 Yr.	2–3 Yr.	3–5 Yr.	5–10 Yr.
Up to 3,000						13						14			
3,000 to 3,500					34†							3			
3,500 to 4,000			20*		21*	9					15				
						16									
4,000 to 4,500				27*	11†	30	39				38	33			
					18*	31						35			
					22*										
					29†										
4,500 to 5,000	1		12*	40†	25†	37*							26		
	8												32		
	10														
	17														
5,000 to 5,500					6†	19									
					7*	23									
						28									
5,500 to 6,000											5	24			2
6,000 to 6,500		4		1											

* Died of heart disease, no evidence of disease in larynx. † Living and well.

With 400 kv., 5 ma., 8 mm. Cu filter, 65–90 cm. T.S.D., and fields 8 × 10 cm. decreased to 3 × 4 cm., 6,500 r were given on the skin in eighteen consecutive days. The tumor dose was calculated to be approximately 4,000 r. Since no mention was made of the depth of the lesion, the 6 cm. and 4 cm. distance previously mentioned was used to arrive at an estimate of the tumor dose. It is realized that the doses may be somewhat higher because of variance in technic.

Cutler's reported results (1) are somewhat better than most. He has 83 per cent three-year survivals in cases with no fixation of the cord and 75 per cent with fixation of the cord. This high percentage of survivals is attributed by Cutler to his technic, yet opportunity to miss the disease is greater with the smaller fields employed. The tumor dose does not approach that of Howes and Platau (4) but is within the average range.

AUTHOR'S SERIES

In the series of 113 cases which form the basis of this paper, 40 involved the cord. For this group the average age was fifty-five years. It comprised 36 white males, 1 Negro male, 2 white females, and 1 Negro female. In Table I the 40 cases of cord lesions are divided into three groups and the patients are designated by case number. The tumor dose is given and each case is listed in the appropriate category with the survival period.

For small lesions of Group 1A the overall three-year survival rate for 19 patients is 63.1 per cent and the five-year rate is 47.3 per cent. No patients with extensive local lesions without node involvement survived three years but in the group with extensive disease and metastatic nodes (Group 1C), 2 of 11 patients lived up to three years and one seven years. All these died of the disease but were remarkably comfortable up to within six months of death, which illustrates the palliative effect of irradiation.

For the 73 patients with lesions exclusive of the cord, the average age was 54.4 years, with 62 white males, 4 Negro males, 6 white females, and 1 Negro female. These cases are shown in Table II. The arrangement is the same as in Table I. It is evident that the majority of these patients were admitted when the disease was advanced; yet a small number were salvaged with x-ray therapy.

For small lesions of Group 2A the three-year survival rate is 22.2 per cent and the five-year rate is 11.1 per cent. For Group 2B the three-year survival rate for 27 patients is 29.6 per cent and the five-year

TABLE II: LESIONS EXCLUSIVE OF CORD: SURVIVAL PERIODS

Tumor Dose, r	Small Lesions					Extensive Local Lesions					Extensive Lesions with Nodes				
	Under 1 Yr.	1–2 Yr.	2–3 Yr.	3–5 Yr.	5–10 Yr.	Under 1 Yr.	1–2 Yr.	2–3 Yr.	3–5 Yr.	5–10 Yr.	Under 1 Yr.	1–2 Yr.	2–3 Yr.	3–5 Yr.	5–10 Yr.
Up to 3,000								47			62	42			
3,000 to 3,500											41				
											44				
											59				
										5†	2		52	64†	
											18			65	
											23				
											61				
4,000 to 4,500	53	1				40*	28		24	49†	66	67	35		46
						60	58		39	57†		68	45		
						70			71†						
						73									
4,500 to 5,000	38	8			48†	17				26†	11	14		33	13†
						25					20	19			
						30*					36	22			
						34					37	43			
						69					63				
5,000 to 5,500	21	50		56*		9				31*	27	32		7	
						51					29				
						55									
5,500 to 6,000	72					16						24			
6,000 to 6,500								3			6	15			
6,500 up						4					12				
						10									

* Died of heart disease, no evidence of disease in larynx. † Living and well.

rate is 18.5 per cent. The greater number of cases in this group may account for the disproportionate percentage as compared with Group 2A. Group 2C, with 37 patients, shows a three-year survival rate of 16.2 per cent and a five-year rate of 6.5 per cent. The over-all three-year survival rate for the entire group of patients is 21.9 per cent; the five-year rate 10.9 per cent.

From Table II it is evident that the majority of patients had extensive disease when irradiation was undertaken. Explanation of this may lie in the fact that hoarseness, the predominant symptom of cancer of the larynx, appears earlier in cord lesions, and none of these lesions was primarily on the vocal cord. The period of delay, until hoarseness or pain demands investigation, permits progress of the disease to a point where the efficacy of any type of treatment is questionable. However, irradiation offers palliation that should not be denied the patient.

In Group 1A, for 1928 to 1936, representing the earlier half of the period covered in this study, the three-year survival rate was 27.7 per cent and the five-year rate was 22.2 per cent. Comparison of these figures with those for the period 1936 to 1944 shows a gain in the three-year rate from 27.7 per cent to 31.3 per cent and the five-year rate from 22.2 per cent to 22.7 per cent. A similar comparison for lesions exclusive of the cord shows just as little variation, so that the improvement in technic and more careful calculation of the tumor dose of later years have had little effect on the survival rate. Since the only perceptible gain appears in early lesions of the cord, it is probable that it is due in part to increased awareness on the part of the public in the recognition of early symptoms. Better diagnosis has, of course, contributed its share.

With a larger number of cases it is possible that these conclusions would be modified somewhat, but most institutions do not have a sufficient number of cases to establish more conclusive evidence concerning tumor dose. The method of analysis used here might make it possible to determine the results more clearly if it were used by others and collective results were evaluated.

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SUMARIO

La Dosis Tumor en el Cáncer de Laringe

Con la idea de que las variaciones en la dosis tumor (carcinoma) durante los 16 años transcurridos entre 1928 y 1944 podrían aportar alguna explicación de las inconsistencias de la respuesta terapéutica, verificóse un estudio de 113 casos de cáncer laríngeo tratados en el Departamento de Radioterapia del Hospital Presbyterian (Nueva York) durante el período mencionado. Los casos fueron clasificados en dos grandes grupos: (1) lesiones de las cuerdas vocales y (2) lesiones situadas fuera de las cuerdas. Ambos grupos fueron subdivididos en tres grupillos de acuerdo con: (A) la limitación de la enfermedad al sitio de origen, (B) difusión a otros tejidos laríngeos sin compromiso ganglionar y (C) invasión ganglionar sobrepuesta. Todos los casos eran de epitelioma escamocelular.

Al principio de la serie, solía administrarse el tratamiento en tres a cuatro semanas, con campos grandes y dosis diarias altas (350 r al aire). Más adelante, alargóse la duración del tratamiento a seis a ocho semanas con campos más pequeños (7 cm. de diámetro), con una dosis diaria más pequeña (125 r al aire a cada uno de dos campos) hasta formar una dosis tumor de unos 5,000 r.

En el Grupo 1A, o sean las lesions limitadas a las cuerdas vocales, de 1928 a 1936, lo que representa la primera mitad del período analizado, el coeficiente de sobrevivencias de tres años fué de 27.7 por ciento y el de sobrevivencias de cinco años de 22.2 por ciento. La comparación de esas cifras con las correspondientes al período 1936–1944 reveló una leve mejora en el coeficiente de tres años, que subió a 31.3 por ciento, en tanto que el de cinco años se elevó de 22.2 a 22.7 por ciento. Una comparación semejante de las lesiones extraplicales no mostró mayor variación, de modo que los perfeccionamientos técnicos y el cálculo más cuidadoso de la dosis tumor en los últimos años han afectado muy poco el coeficiente de sobrevivencia. Como el único beneficio perceptible parece radicar en las lesiones incipientes de las cuerdas, es probable que se deba en parte a mayor tendencia de parte del público a reconocer los síntomas tempranos. El mejor diagnóstico también ha ayudado en ello.

A Consideration of Roentgen Therapy in Producing Temporary Depilation for Tinea Capitis[1]

A New Method

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SINCE 1943, ringworm of the scalp has been epidemic along the eastern seaboard of the United States. MacKee and his associates estimate 5,000 cases in the city of New York (1). An unofficial figure for Philadelphia is 13,000 cases in 1945. In Hagerstown, Md., and adjacent rural communities, out of a total of 8,657 children examined, 565 (479 boys and 86 girls) were infected. Approximately the same number of boys and of girls were examined, yet the incidence was six times as high in boys as in girls (2). There is reason to believe that the epidemic is now abating on the coast, but that the condition will be present endemically in a much higher proportion than formerly, the endemic foci being ready to disseminate the disease widely again if the precautions now in effect in the schools are relaxed. There is every indication, too, that the disease is spreading rapidly inland.

Microsporum audouini is the principal fungus in this epidemic. The infection is spread by infected hairs, and the principal places of contact are the home, the school, the playground, the theatre, and the barber shop, the home and the barber shop being the most likely. It is uncommon for only one child in a family to have the disease; usually all between the ages of four and nine will be infected, due to the indiscriminate interchange of headgear, combs, and brushes. In the Hagerstown epidemic, involved hairs were found in the combs, brushes, scissors, and electric clippers of many of the barber shops, and it is noteworthy that about 65 per cent of the boys had the infection in the "clipper area" only (2). A similar percentage was found in our series, and the location has led many to regard contact with high-back, piled-fabric chairs, often seen in theatres, as the chief offender. In Hagerstown, however, the backs of the seats in the children's favorite motion picture theatres proved to be apparently free of infected hairs (2).

The earliest appreciable lesion is a minute, rounded, scaly patch upon the hair-bearing scalp, the usual location being just within the hair-line at the nape of the neck. The base of the lesion is reddened and hyperemic, but the scales are whitish or grayish in color. The patch slowly increases in diameter, but there is no tendency for involution at the center of the lesion, as in the common types of ringworm infection on other portions of the body. The involved hair shafts become dry and brittle and, in the course of a few days or weeks, many of these hairs break off, leaving a partially bald area studded with broken hairs. A variable degree of itching is present, and excoriation of the lesion may predispose to a secondary infection, such as cellulitis and furuncles and occasionally carbuncles. We have observed deep carbuncles as much as 3 inches in diameter, with multiple draining sinuses. Only rarely is the disease limited to the scaly patches.

A working diagnosis of tinea capitis can be made by examining the scalp under ultraviolet light, filtered through a heavy nickel-glass filter, the so-called "Wood's light" or "Black light." *Microsporum audouini* and *Microsporum lanosum* infec-

[1] From the Department of Radiology, Hospital of the University of Pennsylvania. Presented before the Medical Society of the State of Pennsylvania in September 1946. Accepted for publication in July 1947.

tions have a beautiful and characteristic apple-green fluorescence. If the examination is thorough, one usually finds groups of involved hairs scattered throughout the scalp. The infection may cover most of the scalp or be limited to two or three areas containing a half dozen fluorescent hairs.

The diagnosis is substantiated by culture of the fluorescent hairs upon a potato agar culture medium. The colony characteristics will differentiate between *Microsporum audouini* and *Microsporum lanosum* infections, as will the production of a red pigment in the *Microsporum audouini* colonies.

At the present time, temporary epilation of the scalp by x-rays is the treatment of choice for tinea capitis. This is not a new concept. It has stood the test of time for over forty years. In no other disease has roentgen therapy shown such a favorable percentage of cures over any other type of treatment. It is indeed surprising, in view of the length of time it has been used, the excellent results obtained, and the widespread prevalence of the infection, that this treatment is not more popular and better known to the medical profession. It was first advocated by Freund in 1897 (3). Sabouraud and Noiré controlled an epidemic of ringworm of the scalp in Paris by x-ray depilation beginning in 1904 (4). By 1909, a procedure first advocated by Kienböck and improved by Adamson (5) had become the standard method for depilating the scalp. This is still the one most widely used in this country and is advocated by MacKee as the Adamson-Kienböck technic, or the five-point method (6).

The advantages of x-ray treatment are multiple:

(1) In the proper hands, with adequate equipment, the procedure is painless and so far as we know is harmless to the underlying brain. Permanent alopecia, which is feared by many radiologists and dermatologists, is not easily produced. If it does occur—and it is possible—we believe that in most instances some other factor than radiation is present. Nevertheless, many physicians are hesitant about employing x-ray therapy because of the possibility of medico-legal complications should permanent alopecia result. We believe that alopecia under such circumstances must be rare, and, therefore, have taken the position that as radiologists we should not withhold x-ray treatment from those who need it for tinea capitis.

We have attempted to prevent errors in technic by careful attention to small details. Some of the more common errors include mechanical failures of time clocks, errors in computation of the x-ray tube output, improper calibration of the roentgen-therapy apparatus, and multiple treatment of a single portal. If a permanent alopecia develops in the absence of some error in technic, we believe that there is another cause. Alopecia occurs in conditions where x-ray therapy is not employed and unfortunately very little is known about its etiology. Frequent calibration of the x-ray apparatus, two time clocks, and careful attention to the x-ray factors are essential in employing this method.

2. Appropriate x-ray treatment gives a high cure rate. It is a rare case that is not cured by x-rays. The best results to date from local drug therapy have been recorded in the Hagerstown epidemic (2), where 57 per cent of the cases treated by salicylanilide (5 per cent in Carbowax 1500) or copper undecylenate (saturated solution in Carbowax 1500) were cured. Experience with this method elsewhere has not produced such favorable results.

3. The x-ray treatment can be performed at one sitting. The entire procedure—examination under the Wood's light, planting of the culture, mapping (arrangement) of the scalp, and delivery of the appropriate amount of radiation to the scalp—can be completed in half an hour.

4. The patient becomes practically noninfectious at the end of three weeks. After this period, the entire scalp will be depilated and, for practical purposes, there is no longer any danger of contagion, although some of the organisms may remain in the scalp for several weeks thereafter.

The disadvantages of x-ray treatment are:

1. The possible dangers of permanent depilation, which, as explained previously, are rare and do not constitute a contraindication. If it were not for the medicolegal complications incident to this rare and unexplained sequela, radiologists and dermatologists would be more enthusiastic about the treatment of ringworm of the scalp by x-ray radiation. Under such circumstances, epidemics could be curtailed, psychiatric problems in infected children could be lessened, and absenteeism in schools would often be obviated.

2. Lack of trained technical help, together with lack of interest or timidity on the part of both dermatologist and radiologist to learn the technic and apply it.

3. The cost of the equipment involved. The present initial cost of the equipment is approximately six thousand dollars. Not more than 90 patients can be treated each week under ideal conditions.

4. Irradiation of the underlying brain. The question has arisen: Is there danger to the pituitary gland and cerebral cortex from radiation sufficient to produce temporary depilation? We know of no case, and of no report in the literature, of harmful effects on the underlying brain from such dosage. We have relied upon the general observations of x-ray effects on the skin and other tissues in this connection. The skin tolerates such dosages readily without observable changes either immediate or late. Since brain tissue is reported to be more resistant to roentgen irradiation than skin, we believe the doses that we give are safe.

What cases of tinea capitis should receive roentgen therapy?

It is the feeling of many dermatologists, and statistical results have borne out the impression fairly well, that cases of tinea capitis caused by non-fluorescent organisms—a wide variety of large spore fungi—can be cured by local means and that roentgen depilation is not necessary. In addition, cases due to the animal-transmitted type of Microsporum, *M. lanosum*, are usually cured by chemotherapy. *M. audouini* infections are the most resistant and chronic, and it is these cases that may require roentgen therapy. It is our feeling at this time that depilation in these cases, as soon as they are detected, is the best and the surest means of cure and of prevention of spread of the infection to other children in the family, playmates, and companions in the schoolroom. The public will have to be educated to this point.

PROCEDURE

When it is decided to use x-ray therapy for ringworm of the scalp, the following procedure has been employed by us.

1. The family of the child is told about the natural history of the disease and what may be expected from x-ray treatment. Many fathers and mothers are hesitant about giving permission for the treatment after being told that temporary depilation lasts for three months and that rarely a permanent depilation will occur. Thus far we have been able to assure tham that we have not had a single case of permanent baldness.

2. Local treatment is discontinued for at least one week before the x-ray depilation is undertaken. Otherwise, unnecessary reactions are produced. Many of the local fungicides are irritating, some of them being strong enough to produce widespread vesiculation upon the scalp.

3. The child is brought to the x-ray department with the hair clipped short to the scalp. Closely shaving the head is undesirable, as will be discussed later.

4. The head of the child is carefully inspected, the portals are marked out upon the scalp with ink, and the treatment is administered.

Our technic requires approximately twenty to twenty-five minutes. As previously pointed out, the treatment is painless. Children over the age of five usually co-operate beautifully and will hold perfectly still while the procedure is carried out. We have depilated children as young as thirty months. For some of the more excitable ones, the oral administration of 1 grain of phenobarbital about forty-five

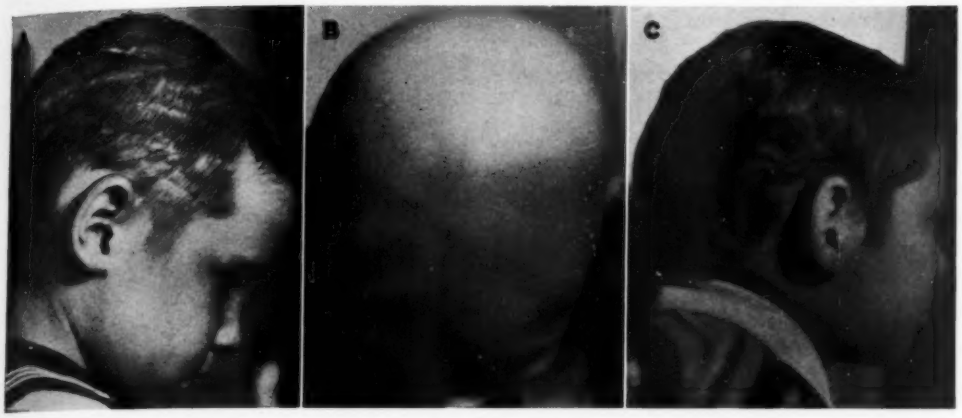

Fig. 1. A. Patient before depilation with hair clipped short, showing normal thickness of hair. B. Same patient six weeks after irradiation and three weeks after defluvium. Every hair is out. C. Same patient seven months after irradiation and four months after first hair regrowth was noted. The hair is a little finer in texture than normal but its thickness is equal to that shown in A.

minutes before the radiation is administered has been most helpful.

When the irradiation is completed, the parents are instructed as to the care of the scalp and the patient is asked to return at the end of three weeks. There are usually some fever and restlessness, with loss of appetite, during the first twenty-four hours after irradiation. These symptoms may be due to radiation sickness. Early in our series, there were two instances of severe secondary infection superimposed upon the fungus. One child had at least nine carbuncles, 2 to 5 cm. in diameter, scattered over the head. In this case there was a fever of 105° F. for twenty-four hours after treatment, with toxic manifestations and delirium, and a soft, extremely tender posterior cervical adenopathy for approximately one week after treatment. Because of instances of apparent dissemination of infection after irradiation, no subsequent patients with severe secondary infection were treated until this had been controlled.

The defluvium has occurred as early as the thirteenth day and as late as the twenty-first day; in the average case appreciable loss of hair is noticed about the sixteenth day. It is at this time that the condition is most infectious and a stocking cap is advised to prevent promiscuous scattering of hair. On the twentieth day an adhesive strapping is applied to the head and the remaining hairs are removed. All the loose hair should be gathered carefully and burned, as the organism is quite resistant. Some of our specimens of hair for culture which were misplaced for over one year produced as rapid and characteristic growth on the potato agar medium at the end of that time as did newly plucked hairs (7). Whether or not these organisms retained their virulence is not known.

The hairs are usually easily removed by the adhesive strapping but if the head has been closely shaven, many of them cannot be grasped and the adhesive can get no purchase upon them. In addition, many of the diseased hairs are broken off flush with the scalp and will remain in place unless removed by a depilatory wax. We use the epilating wax of Pusey (8), a mixture of finely powdered rosin (four parts by weight) and beeswax (one part by weight). This is heated and spread on a smooth piece of old linen. It has the consistency of an ordinary glue. After cooling somewhat, it is pressed carefully into the scalp and allowed to remain ten or fifteen minutes until it is hard. It is then stripped off and in most instances removes all remaining hairs. This method has decided advantages over adhesive taping, but it is cumbersome to use and some practice is re-

quired on the part of the parents to achieve a clean scalp. This mixture is available commercially in most drugstores as the ordinary depilatory wax.

After all of the hair has been removed from the head, the child is not infectious. It has been found that local treatment is not necessary after depilation.

The child is completely bald for about six weeks, after which a fine, fuzzy growth of new hair makes its appearance. This is not of the character of that seen after shaving the head, but is more like the first growth of hair upon a baby who is born bald. A certain percentage of the hairs spring up rapidly and grow at a normal rate. Each week the number of hairs increases, reaching normal during the next six months (Fig. 1).

The scalp is usually dry during the first four or five months, since the amount of irradiation given is sufficient to produce temporary inactivation of the sebaceous glands. The normal oiliness is regained within one year after treatment. The head can be kept clean by a warm olive oil massage twice a week at bedtime, followed by a castile soap shampoo in the morning. In none of our cases have dryness and scaling of the scalp persisted more than six to eight months after irradiation.

The hair is usually unchanged in color or may be slightly darker when it has regrown. The texture is always the same as before irradiation. In Negro children, the new hair is frequently straight or only slightly wavy, but resumes the usual kinky appearance within the year. In white children, in numerous instances, originally straight hair has become quite curly after irradiation. This change has persisted to date, but whether the effect will be permanent we do not know. In several children, irradiation has been followed in the next week by measles, but this has not been known to retard the re-growth of the hair in any instance.

The children are followed for a period ranging up to one year, *i.e.*, until hair regrowth is complete, the scalp has returned to its normal appearance and three months have elapsed after the removal of the last fluorescent hair.

Five-Point Technic: Roentgen therapy for tinea capitis has been standardized in the United States for the past thirty years. The five-point Adamson-Kienböck technic, as standardized and popularized by MacKee and his associates, has been used in tens of thousands of cases without untoward results and with a high cure rate. With this technic, five points for centering the x-ray beam are selected in the following manner: Two points in the sagittal mid-line, exactly 10 inches apart and at an equal distance within the anterior and the posterior hair-line, are marked off. A third point is marked off in the mid-line exactly 5 inches from both the front and the back mid-line points. From this third point, perpendicular lines are dropped to either side of the mid-line so that the resulting cross forms four angles of 90 degrees. Five inches to the right and 5 inches to the left of the mid-line, approximating the top of the auricle, another centering point is made. Each of these five points is exactly 5 inches from the adjacent points and the lines of irradiation from adjacent portals are always perpendicular to each other.

The distance between the x-ray tube target and the scalp is fixed at 25 cm. MacKee delivers 300 r (1 skin unit, unfiltered) at 60–100 kv. to each of the five areas. No attempt is made to shield the surrounding areas when any one portal is being treated. Therefore, the vertex of the scalp, although having its own portal, receives some irradiation from both the anterior and posterior and the two lateral portals; similarly, a lateral portal will receive some irradiation when the posterior, anterior, and vertex portals are treated. Thus, while the dose delivered to the five centering points will be 300 r, considerably more will be delivered to the areas intermediate between these. It has been determined by physical measurements of wax models that some of the areas where the overlapping is the greatest will receive as much as 180 per cent of the dose delivered to the center of the portal (5).

Authors' Technic: MacKee considers 300 r an epilating dose for children, but we have found this amount insufficient to produce complete depilation. The areas of failure in the standard five-point technic are over the centers of the anterior and posterior portals, where the incidence of scattered and overlapping radiation from the other portals is lowest. Even with a dose as high as 350 r to each of the five areas, we frequently failed to produce depilation over the centers of the fields, particularly in the anterior portion, where there might be a fringe of hair 2 or 3 cm. wide at the anterior hair-line. As a result several cases were not cured and, since it was estimated that some areas of the scalp had received as much as 180 per cent of 350 r, *i.e.*, 630 r, it was thought unsafe ever to repeat the depilating dose.

After the above failures, an attempt was made to evolve a technic which would make possible larger, more uniform doses to individual areas and yet cut down on the total dose delivered to any one portion of the scalp. By selecting relatively flat surfaces of the head and shielding the surrounding area with lead as each individual portal was treated, a higher dose could be delivered to the surface under treatment without exposing the surrounding areas as in the Adamson-Kienböck method.

It became apparent at this time that no single standardized technic for separating the various areas of the scalp was possible if the areas were to be treated as shielded portals. The open field treatments are all based upon arithmetical and trigonometric measurements designed to give a fairly even dosage over a sphere, but the child's head is not a sphere. The hair-bearing areas usually consist of four to six fairly flat plateaus joined together at rather acute angles.

Fig. 2. Authors' closed-portal technic. A. Lead shield fitted closely to the borders of the area to be treated over the vertex of the head. Lead is in contact with the scalp all around the area to be treated. B. Lateral view showing position of cone for treatment of the portal shown in A.

In the most common type, the anterior and superior portion of the head forms a broad, flat plateau with an abrupt angulation at the vertex. From the vertex to the superior border of the occiput is another fairly flat surface, and from the occiput to the nape of the neck, the musculature forms a third flat surface when the head is in the neutral or slightly flexed position.

Viewing the head from the front, one notes that the flat anterior plateau is at a rather sharp angle to very flat surfaces forming the general temporal areas of the skull. Thus, in the average child's head, there are five areas which lend themselves

readily to shielding along the angulations between them. In some heads, the angulation between the vertex plateau and the occiput is almost non-existent and in such cases four fields may be used: two lateral, an anterior, and a vertex occipital. In children with a low hair-line, it may be necessary to add a sixth area to produce complete depilation along the anterior hair-line.

When the patient presents himself for depilation, the edges of the various plateaus are carefully plotted with red ink upon the closely cropped scalp. A large variety of lead shields have been gradually accumulated, so that a plateau of any of the common dimensions can be closely fitted with a lead shield around its border (Fig 2). Additional lead is always on hand, so that any variation in size or shape necessitates but a few minutes delay while a new shield is cut from $^1/_{32}$-inch lead sheeting. The x-ray therapy tube is equipped with the common truncated cone, whose lower diameter is sufficient to cover any area of the plateaus that will be encountered. The cone is placed so that the lower edge is on a level with the highest point of the plateau and the central point is directly over the center of the plateau. Further angulation of the cone in the left-right and antero-posterior axes equalizes the difference in height between the four corners of the plateau, with an imaginary plane drawn through the lower border of the cone. This difference in height is usually less than 4 cm. After the appropriate dose of radiation is delivered, the edge of each area is carefully marked off in black ink to indicate the actual field treated and to define the edge for treatment of the adjacent area.

A heavy duty intermediate voltage water-cooled therapy tube, operating on a Villard circuit is used, with the following factors: 75 kv.p., 18 ma., no added filtration, focal skin distance 26 cm. The output is measured in air at 220 r per minute.

Each field is given 500 r (in air). This dosage is based on actual experimentation. At 440 r, with the above factors, only the center of the portal was depilated, hair remaining all around the margin of the portal. Three hundred roentgens did not produce a 1 cm. circle of alopecia even in the center of the field.

Measurement with a water phantom on some typical arcs of the plateaus has shown the dose at the periphery or at the border of the plateau to be 75 per cent or 375 r. The dose to each central area is 500 r (in air), which is the largest dose delivered to any one area in the scalp, the amount gradually falling off as the periphery is approached. Such a dose produces a complete and uniform temporary depilation over the entire hair-bearing scalp.

With the Adamson-Kienböck technic, Osborn *et al.* (9) state that the dose to the central area is 300 r measured in air. This is the smallest dose delivered to any one area, the amount increasing to 540 roentgens at the points of maximum overlap. Thus, we are actually delivering less radiation to any one portion of the scalp.

In some instances we have had a 2 or 3 mm. overlap resulting in double treatment over a narrow strip. These fine strips have shown pigmentation after a period of three weeks, but hair growth has been just as rapid as elsewhere on the scalp.

During the last two years, in the Radiological Clinic of the Hospital of the University of Pennsylvania, over 160 children with tinea capitis have been treated by this closed-portal method for temporary roentgen depilation. In 120 cases a twelve-month period has elapsed since depilation; only one failure has been observed to date. None of these patients has shown any localized or complete permanent alopecia. According to the parents' statements, the hair is of equal texture and is as thick as the original hair. The scalp has regained its normal oiliness and there is no untoward pigmentation of the surrounding skin. In the case regarded as a failure, the hair re-growth was normal, but the infection persists.

Thus far no cases have been treated by local or "spot" depilation. Numerous previous studies have shown the futility of

such procedures, but we plan to re-explore its possibilities.

In presenting this report on irradiation in tinea capitis, the authors feel with many others that if some safe method other than x-ray therapy can be developed to cure ringworm of the scalp, radiation should never be employed. On the other hand, as long as radiation is used as a form of treatment, one should utilize factors that will accomplish the desired result and at the same time reduce the volume of radiation being absorbed in the skin and underlying tissues.

SUMMARY

1. Tinea capitis is epidemic in the Eastern United States.
2. Depilation by roentgen therapy is the method of choice for cure in the cases infected with *Microsporum audouini*.
3. Description of a closed-portal technic individualized to varied head shapes is presented.
4. Of 120 cases with a twelve-month follow-up period, all except one have been cured without any resultant damage to the hair or the scalp.

NOTE (March 1948): Since the preparation of this paper we have learned that the Department of Dermatology of the Hospital of the University of Pennsylvania is curing 50 per cent of cases of *M. audouini* tinea capitis in four months, and anticipate 95 per cent cures in nine months, by local application of 5 per cent salicylanilide, 5 per cent zinc undecylenate, and 20 per cent undecylenic acid in an appropriate base. It is our policy at this time to limit roentgen depilation to those cases in which such a course has failed.

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SUMARIO

Consideración de la Roentgenoterapia en la Tinea Capitis: Nueva Técnica

Desde 1943, la tiña del cuero cabelludo ha sido epidémica en los niños a lo largo del litoral oriental de los Estados Unidos. La depilación del cuero cabelludo con los rayos X da un alto porcentaje de curaciones y constituye el procedimiento de elección para los casos debidos al *Microsporum audouini*.

Los AA. han utilizado una nueva técnica de "puerta cerrada," basada en la observación de que las zonas vellosas del cuero cabelludo del niño constan de varias mesetas bastante planas formando ángulos algo agudos entre sí. Esto permite emplear pantallas de plomo para proteger las zonas adyacentes mientras se trata una meseta dada. La dosis máxima entregada en el punto central de cada meseta es de 500 r. El tratamiento de todo el cuero cabelludo se ejecuta en una sola sesión, lo cual exige menos de media hora.

En 120 niños tratados con esta técnica y mantenidos en observación por un año, sólo hubo un fracaso en lo tocante a erradicar la infección. Ninguno de los enfermos ha mostrado alopecia, ya total o localizada, ni otros efectos contraproducentes.

Additive Effects of X-Rays and Methylcholanthrene in Inducing Mouse Leukemia[1]

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AGENTS OF THREE general types, one physical and two chemical, have been shown to be leukemogenic for mice. These are ionizing radiations, such as x-rays and gamma rays (1–3), carcinogenic hydrocarbons, as for example methylcholanthrene benzpyrene and 9,10-dimethyl-1,2-benzanthracene (4–7), and various estrogens (8, 9). In susceptible stocks the effectiveness of these agents is proportional to the dose used, varying with the genetic constitution of the strain of mice (3). Furth and Boon (10) reported synergistic effects of combined application of methylcholanthrene and irradiation with x-rays, but Kaplan and Kirschbaum (11) were unable to demonstrate synergism of these agents for other stocks of mice. However, in the latter experiments very potent doses of each agent were used, and it is probable that under such circumstances neither additive nor synergistic effects may be obtained. McEndy, Boon and Furth (12) did not observe additive effects when very large doses of each agent were used.

The purposes of the experiments to be reported here are the following:

1. To confirm the observation that two leukemogens may, when applied simultaneously to mice in greater than threshold doses, have additive effects.
2. To show that the phenomenon of additive effects of two leukemogens probably depends upon susceptibility of the strain of mice to the independent action of each of the leukemogens.
3. To demonstrate the importance of genetic constitution in determining leukemogenesis.

MATERIALS AND METHODS

The x-ray-treated mice were exposed to general body irradiation in cardboard boxes at 30 cm. target-skin distance, 140 kv., and 2 mm. aluminum filter, h.v.l. 4.2 mm. Al. All doses are given as roentgens in air at the surface of the mouse. Carcinogen-treated mice were skin-painted three times weekly with a 0.25 per cent solution of methylcholanthrene in benzene. A camel's-hair brush, 3/8 by 5/8 inches, was used, a different site being chosen for each successive painting to decrease the number of induced skin tumors.

Four groups of strain dba mice (subline 212) are included in this study, as follows:

I. Thirty-four mice received a total of 1,100 r of x-rays in eleven weekly treatments of 100 r. The mice were ten weeks of age at the time of first exposure.
II. Thirty-four mice received eighteen skin paintings of methylcholanthrene, the first painting at fourteen weeks of age.
III. Forty-eight mice received both treatments—x-rays (total of 750–1,100 r) beginning at ten weeks and methylcholanthrene at fourteen weeks of age.
IV. Ninety-two controls received neither x-radiation nor methylcholanthrene.

Four groups of strain CBA mice were put on experiment as follows:

[1] From the Departments of Radiology and Anatomy, University of Minnesota Medical School, Minneapolis, Minn. This investigation has been aided by grants from The Jane Coffin Childs Memorial Fund for Medical Research, The National Cancer Institute, and the Cancer Fund of the Graduate School of the University of Minnesota. Presented at the Thirty-third Annual Meeting of the Radiological Society of North America, Boston, Mass., Nov. 30–Dec. 5, 1947.

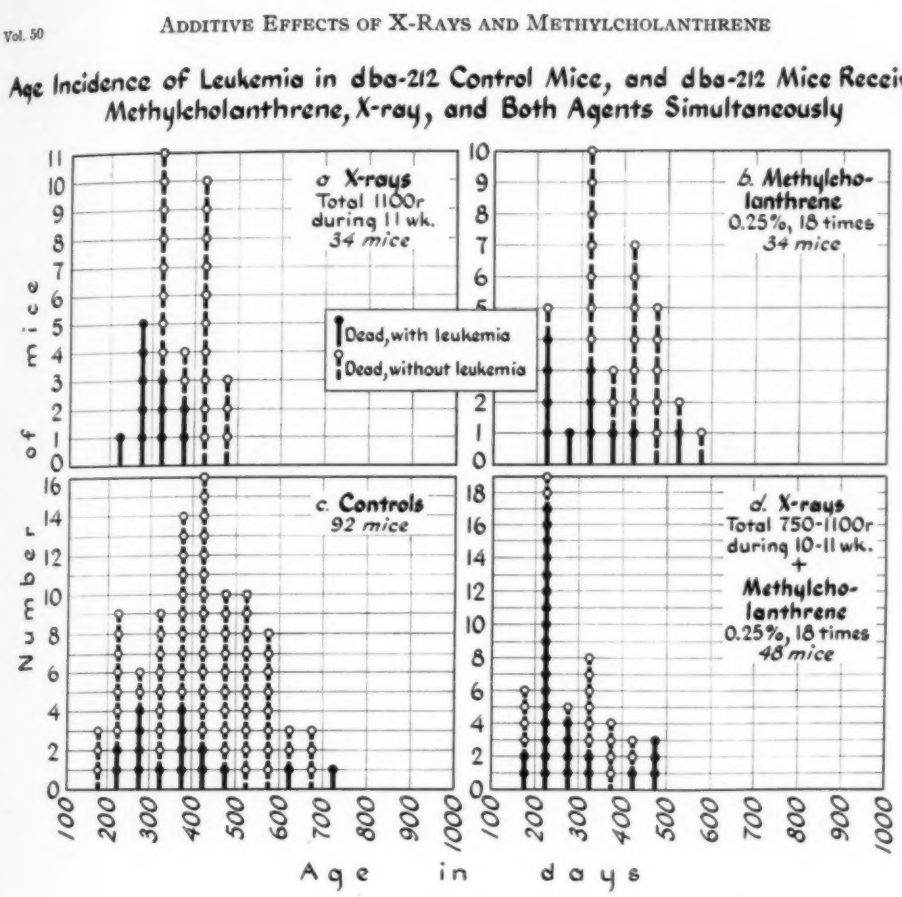

Fig. 1.

I. Twenty-one mice received 500 r in ten weeks (50 r × 10) and 5 animals received 750 r (100 r × 5 and 50 r × 5). Mice were ten weeks of age at first exposure.

II. Thirty mice received eighteen skin paintings of methylcholanthrene, the first painting at fourteen weeks of age.

III. Twenty-six mice received the combined treatment of 500 r and methylcholanthrene and 8 mice received 750 r plus the carcinogen, irradiation being started at ten and methylcholanthrene at fourteen weeks of age.

IV. Eighty-four controls received neither x-radiation nor methylcholanthrene.

Mice of the dba strain (subline 212) are moderately susceptible to spontaneous leukemia; 16 cases occurred in 92 controls at an average age of 378 days (Fig. 1, *c*). These animals are also susceptible to the induction of leukemia by x-rays and methylcholanthrene in the doses employed in these experiments (Fig. 1, *a* and *b*).

Mice of the CBA strain also show some susceptibility to spontaneous leukemia, 9 cases occurring in 84 controls at an average age of 720 days (Fig. 2, *c*). This strain is, however, resistant to the leukemogenic action of methylcholanthrene in the dose used in these experiments (Fig. 2, *b*), but very susceptible to the leukemogenic action of x-rays (Fig. 2, *a*).

The animals were regularly observed (at least once a week) for evidence of leukemia.

Diagnosis was usually made antemortem and was confirmed by gross examination at autopsy, and by microscopic study in doubtful cases. Leukemia and lymphosarcoma are grouped together as *leukemia*. All animals received the same diet, Purina fox chow, and were maintained in the same room in adjacent cages.

OBSERVATIONS

In strain dba, combined treatment with x-rays and methylcholanthrene resulted in the induction of relatively more cases of leukemia (at an earlier age) than were caused to appear by either agent used independently (Fig. 1, *d*. Compare with 1, *a* and 1, *b*). Each of the leukemogenic agents, when used alone, induced an appreciable number of leukemias (which appeared early) as determined by comparison with controls (Figs. 1, *a*, *b*, *c*).

In strain CBA, combined treatment resulted in the induction of relatively the same number of leukemias as in the group treated with x-rays alone (Fig. 2, *d*. Compare with 2, *a*). If anything, the incidence was actually lower when both agents were used simultaneously. Although CBA mice are very sensitive to the leukemia-inciting activity of x-rays, they were resistant to a dose of methylcholanthrene which was effective in inducing leukemia in dba mice (Fig. 2, *b*. Compare with 1, *b*). Experiments now in progress in our laboratory indicate that as few as 6 skin paintings with methylcholanthrene induce leukemia in dba mice.[2]

Control mice of the CBA strain were longer-lived than controls of the dba stock (compare Figs. 2, *c* and 1, *c*). Spontaneous leukemia appeared earlier in the stock of shorter life expectancy (Figs. 1, *c* and 2, *c*). Although x-rays represented a more potent leukemogen in strain CBA than in strain dba, from the standpoint of number of cases induced, the latent period of induction was longer in the strain (CBA) with the longer life expectancy. Of 18 CBA mice given 100 r weekly for eleven weeks, 14 showed leukemia at an average age of 402 days (range: 244–574). Among 34 dba mice treated with the same dose of x-rays in the same manner, leukemia appeared in only 13 but at an average age of 303 days (range: 225–375). Spontaneous leukemia has been observed to appear later in the long-lived hybrids between a high and low leukemia stock than in the relatively short-lived high-leukemic strain (13).

[2] Additive leukemogenic effects are being obtained in dba mice receiving relatively small doses of x-rays (200 r) and methylcholanthrene (6 skin paintings).

DISCUSSION

Although a stock of mice (CBA) is susceptible to the action of a leukemogen such as x-rays, it may not respond to the leukemia-inciting action of methylcholanthrene. This suggests that different genes control susceptibility to different agents. The dba stock possesses genetic susceptibility to both agents, whereas the CBA stock is susceptible to only one, x-rays. There are, however, grades of susceptibility to a single leukemogenic agent, *e.g.*, certain stocks are far more susceptible than others to x-rays.

The additive effects of x-rays and methylcholanthrene in the dba strain indicate that the basic mechanism of induction of leukemia is probably the same for the two agents. Where additive effects were not obtained (in the CBA strain), it may be assumed that the mice responded to one, but not the other agent.

The long latent period for x-ray-induced leukemia in CBA mice (as compared with dba) can be correlated with (*a*) a later onset of *spontaneous* leukemia, and (*b*) longer life expectancy. This suggests a fundamental difference in the metabolism of these two strains, and these differences appear to influence the rate at which leukemic (cancerous) and certain non-leukemic processes (as reflected in longevity) develop.

SUMMARY

Two leukemogenic agents acted in an additive fashion, when administered simultaneously, in a stock (dba-212) susceptible to the leukemogenic action of each of these agents. This effect was not apparent in

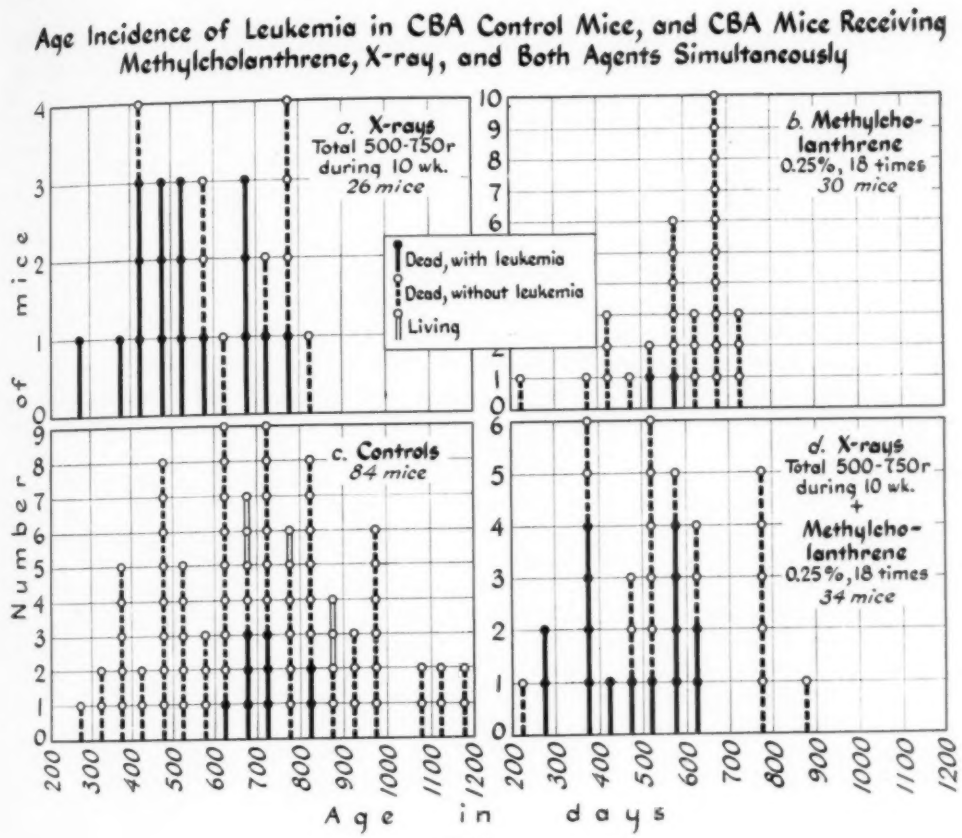

Fig. 2.

CBA mice, which were susceptible to the leukemia-inciting activity of one agent (x-rays) but not the other (methylcholanthrene). These results suggest that susceptibility to each of two leukemogens (x-rays and methylcholanthrene), when used singly, is essential for demonstration of additive effects. The interaction of multiple agents may be involved in the genesis of both spontaneous and induced leukemia. The effectiveness of these agents in inducing the disease is dependent on the genetic constitution of the test animals. Longevity of two strains of mice was correlated with the length of the latent period of induction of leukemia by x-rays.

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SUMARIO

Efectos Aditivos de los Rayos X y el Metilcolantreno en la Inducción de Leucemia Murina

Dos elementos leucemógenos obraron aditivamente, al ser administrados simultáneamente, en una raza (dba-212) de ratones susceptibles a la acción leucemógena de cada uno de ellos. Dicho efecto aditivo no se manifestó en ratones CBA que eran susceptibles a la acción leucemógena de uno de esos agentes (rayos X) pero no del otro (metilcolantreno). Este resultado sugiere que, para la obtención del efecto aditivo, es esencial que haya susceptibilidad a cada uno de los dos leucemógenos (rayos X y metilcolantreno), usados por separado. En la génesis de la leucemia, tanto espontánea como provocada, puede intervenir la interacción de muchos agentes. La efectividad de los mismos en la producción de la enfermedad depende de la constitución genética de los animales de ensayo. La longevidad de las dos cepas de ratones usados se correlacionó con la duración del período latente de inducción de la leucemia por los rayos X.

The Practical Aspects of the Diagnosis, Treatment, and Prognosis of Hodgkin's Disease and Allied Disorders[1]

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TO COVER ALL aspects of Hodgkin's disease and allied conditions in twenty minutes is a task of some magnitude. If I seem dogmatic, please believe me when I say that I really do not feel dogmatic at all. It is simply that in the time allotted one cannot surround all that one says with the *ifs*, *buts*, and *whereas's* that really should be there. The more I see of these conditions—these that kill and maim the young and the old—the more humble I become in their presence, and, indeed, I have an uncomfortable feeling that the more I see of them, the less I really know.

For many years at the Mallory Institute of Pathology and in the Thorndike Memorial Laboratory, Dr. Frederic Parker and I have used a classification which differs only in minor respects from that of many competent pathologists elsewhere. We believe that this classification is simple, that it is in accord with the facts, and that it has stood the test of time. We believe that it is wrong to lump (this word is used advisedly) all the various types under the rather vague and actually meaningless term malignant lymphoma, though we ourselves have so erred. The different types of Hodgkin's disease and allied disorders occur at various ages, have different symptoms, and behave quite differently to our therapeutic approaches. The prognosis of each type differs from that of the others. These facts alone may justify the classification.

Hodgkin's disease itself we divide into three types: the comparatively benign paragranuloma, the more frequent and more fatal granuloma, and the rare but extremely malignant sarcomatous type, not recognized by all but first described by Ewing, a formidable antagonist and a brilliant pathologist. It has repeatedly been shown (by multiple biopsies) that the paragranulomatous type may progress into the granulomatous and that this latter in turn may on rare occasions change into the sarcomatous form. A reversal of this sequence never occurs.

Then we have the universally accepted, though variously named, giant follicle lymphoma originally described by Brill, Baehr and Rosenthal. Like Hodgkin's paragranuloma, it is often a prelude to adventure, for all are agreed that a considerable percentage of these cases eventually change into one of the more malignant tumors such as lymphosarcoma or Hodgkin's disease. This metamorphosis into a more malignant disease may be seen in some small portion of an excised node when the patient first comes under observation, or it may occur months or years later. Of 25 of our cases showing the characteristic picture of giant follicle lymphoma, 15 eventually changed into some more malignant form.

Lymphosarcoma is recognized by all, but unfortunately many physicians play fast and loose with this term, some using it to include practically the whole group of diseases of which we are now speaking, others—and we are of that school—confining the term sharply to a malignant, invasive tumor, the type cell of which is the lymphocyte or the lymphoblast.

Reticulum-cell sarcoma also belongs in this general group. It is a true tumor and may be generalized, involving many or-

[1] From the Thorndike Memorial Laboratory and the Second and Fourth (Harvard) Services, Harvard Medical School, and the Mallory Institute of Pathology, Boston City Hospital. Presented at the Thirty-third Annual Meeting of the Radiological Society of North America, Boston, Mass., Nov. 30–Dec. 5, 1947.

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gans. More rarely it may be primary in and confined to bone. The generalized type is far the more common. That primary in bone was first described by Dr. Frederick Parker and myself in 1939 and in the same year was accepted as a specific entity by the Registry of Bone Sarcoma of the American College of Surgeons.

Finally, in this general class of disease there should be included plasmocytoma and endothelioma. Of the former I shall have little or nothing to say. Of the latter I should say this: it is one of the commonest lymph node tumors in Java and there, I believe, you must go to see it. We have not encountered a case in twenty-five years nor is there one among the 19,000 autopsies at the Boston City Hospital.

Of all these diseases, Hodgkin's granuloma is the most frequently encountered and it is a fair approximation to the truth to say that for every 250 cases of Hodgkin's granuloma there will be 100 of reticulum-cell sarcoma, 60 of lymphosarcoma, and perhaps 50 each of Hodgkin's paragranuloma, Hodgkin's sarcoma, and giant follicle lymphoma. I cannot give you reliable statistics for the relative frequency of plasmocytoma.

Hodgkin's paragranuloma and Hodgkin's granuloma may occur at any age from infancy to extreme old age and, indeed, do occur with approximately equal frequency in each of the first seven decades. Hodgkin's sarcoma never, so far as we know, appears before the age of twenty-five and in general it follows the curve of malignant disease, being most frequent in the fifth and sixth decades. The same may be said of generalized reticulum-cell sarcoma, but one must remember that primary reticulum-cell sarcoma of bone not infrequently occurs in the teens. Giant follicle lymphoma seldom, if ever, is seen before the age of twenty and appears to be more frequent in the older age group. The age incidence of lymphosarcoma is, so to speak, diphasic, for it occurs first in childhood and then reappears in the sixth decade. It is practically unknown in the twenties and thirties and is not common even in the forties. Plasmocytoma is a disease of middle or old age. I can say nothing of the age incidence of endothelioma.

One word as to diagnosis. The only method of making a precise diagnosis is by the microscopic examination of properly fixed, adequately stained tissue presenting the lesion in question. Dr. Ewing was wont to wax eloquent, and a bit more, on the impossibility—yes, the impossibility—of making a correct diagnosis by any other method. It is not for the clinician to dictate to the surgeon precisely which node to remove. It does, I believe, lie within his province to say which node he would like to have taken out, provided the surgeon believes he can get it out with a modicum of ease and safety to the patient. Small satellite nodes rarely show the lesion in question. They should be avoided. Do not cut through a node in order to remove a portion. Nine times out of ten all will go well; the tenth time it will grow out into the incision like a courageous mushroom and the patient will be a doctor's daughter.

If I start on symptoms, the sun will go down. Perhaps the best and the truest one can say is that with any of these conditions one may have practically any symptom or sign—those of eye, ear, nose, throat, genito-urinary tract, skin, blood-forming organs. Indeed, one may have any symptom and any sign, and that follows as the night the day, for lymphoid tissue occurs anywhere. I have often said that in this general group there was not a single sign or symptom that had not been seen and a student asked, "Have you ever heard a diastolic murmur?," to which I answered, "Once—in a reticulum-cell sarcoma involving the mitral valve." A little far-fetched, yes, but it emphasizes the extraordinarily protean character of the symptomatology of these conditions. The symptoms of the different types vary considerably. Thus pain is never seen in Hodgkin's paragranuloma while it is present, sooner or later, in close to 70 per cent of cases of reticulum-cell sarcoma. Time

prohibits my going into this very interesting subject of symptomatology.

The most important thing, of course, is treatment. Right off let me say that I personally believe that the radiologist and the clinician should care for the patient conjointly and together. It is not proper for the clinician to tell the radiologist exactly what dose of x-ray to give, because he does not really know, and I do not think it is proper to turn the patient over to the radiologist entirely, because he is not quite as familiar as is the internist with the general signs and symptoms of the particular case being followed. I think the radiologist and the clinician should treat the patient together, and that has been my custom for twenty-five years.

Hodgkin's paragranuloma, if sharply localized to one area, should, in my opinion, be excised and thereafter a moderate dose of radiation should be given to the involved area. If the disease is generalized, that is, for instance, if it is in both sides of the neck, or if internal structures such as mediastinal nodes are involved, moderate doses of x-ray are sufficient. If symptoms indicating widespread involvement should arise, such as fever, anemia, or a high white count, it is probable that the condition is changing over into Hodgkin's granuloma and then one has that much more formidable condition to treat.

In Hodgkin's granuloma, if the disease is very sharply localized to an easily accessible region and if, further, there are no general symptoms such as fever, anemia, or the like, I believe radical excision followed by radiation may be advised on very rare occasions. If the condition is generalized, as it usually is by the time we see the patient, I think a moderate amount of x-ray to appropriate areas is the best treatment. I do not believe in the very heavy doses advocated by some. I have used very heavy radiation in one instance only, and that in the case of a physician who insisted that he be so treated. The results were no better than those usual with moderate dosages. X-ray is, as it were, like a reverse bank account: you can take out just so much money and then it is all gone; you can give just so much x-ray and then you can't give any more.

Anemia of significance, if present, must be vigorously treated by transfusion; if it is present prior to x-ray treatment, transfusions should be given before irradiation is begun. Iron in full doses is occasionally valuable, especially if the patient's diet has been inadequate. Extra vitamins are rarely called for unless there is a clear-cut vitamin deficiency. The psychological care of the patient is of the utmost importance, but we have no time to discuss it in detail. Suffice it to say that the fear of suffering and the fear of death are often a greater trial than these things themselves.

In the third place—and this I have been taught by my residents—continue therapy until it is perfectly clear that further treatment can do no good. Some day that point will be reached, but it is astounding how often one sees a patient for whom there appears to be no hope, and a young, enthusiastic resident will urge still further treatment; you accede to his demand, and then two weeks later, when you say, "Who's that?," he says, "That's the fellow you said was going to die!" Remember, also, that a patient may have another entirely unrelated disease. Just because he has Hodgkin's granuloma does not mean he may not have something else requiring careful attention. Serious errors can be made if one forgets this fact. A simple prostatectomy relieved the symptoms in one patient and a cholecystectomy for gallstones relieved the pain in another. In each I must confess that I personally had erroneously attributed the symptoms to Hodgkin's disease.

In cases of Hodgkin's sarcoma, I think the best treatment is to make the patient comfortable and hope you are wrong. It is true that this tumor will, not infrequently, respond dramatically to radiation. But the response is only temporary and we have never seen a patient live three years from onset. Most of them are dead within a year.

Giant follicle lymphoma, I believe,

stands in the same category, so far as treatment is concerned, as Hodgkin's paragranuloma, but remember that many cases change over into other more malignant forms such as lymphosarcoma, requiring more intense treatment.

In twenty-five years I think we have seen about thirty adult cases of lymphosarcoma. If it is localized, as it only rarely is, let us say to the stomach, a very wide excision may result in what appears to be a cure. We personally have never had such a case of our own, but I know that surgeons have had such cases and their patients appear to be cured and, as the condition is otherwise so rapidly fatal, such radical procedures are justified. If the condition is inoperable, the proper amount of x-ray is all that can be offered, and radiation, in our experience, has been of temporary benefit only.

If reticulum-cell sarcoma is localized to an accessible region, excise very widely and hope for the best. I know of one patient who eleven years ago had what was thought to be an inoperable carcinoma of the cecum. Actually it was a reticulum-cell sarcoma and, though it had already extended to the regional nodes, it was excised *in toto* by a courageous surgeon. That patient is alive, well and free from symptoms today. Had that surgeon not acted as he did, the man would not be alive. If the disease is localized but not operable, I believe very heavy radiation should be given; if generalized, sufficient x-ray to alleviate symptoms is indicated.

Reticulum-cell sarcoma of the bone we have not seen much of, but what evidence there is indicates that amputation followed by radiation to the local nodes is the therapy of choice. Although the tumor has a very malignant appearance, it is very definitely curable. It can be diagnosed by biopsy only.

I have not had sufficient personal experience with the mustard gases to allow me to comment on their use.

We have but little time left for prognosis. Hodgkin's paragranuloma, if it does not change, is compatible with many years of active life. One patient has survived thirty-five years. Hodgkin's granuloma is much more malignant. Perhaps 10 per cent of the patients die five to ten years from onset. Yet over 40 per cent of our living patients have had their disease for this length of time. Only very rarely do such patients live longer. Reticulum-cell sarcoma may be cured by surgical intervention. Probably 50 per cent of the patients die within a year; yet of our living patients, 25 per cent have had their disease from five to ten years. Hodgkin's sarcoma kills in a year or two.

Lymphosarcoma, unless cured by surgical intervention, kills within three years; often, especially in children, in a few months.

Giant follicle lymphoma is very unpredictable. If it remains unchanged, the patient may live for years. If metamorphosis into another form occurs, the prognosis is of that form. Sudden death may occur in any form.

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SUMARIO

Aspectos Prácticos del Diagnóstico, Tratamiento y Pronóstico de la Enfermedad de Hodgkin y los Trastornos Afines

La enfermedad de Hodgkin puede dividirse en tres formas: el comparativamente benigno paragranuloma; el más frecuente y más letal granulóma; y el raro, pero sumamente maligno, tipo sarcomatoso. Los estados afines comprenden: linfoma folicular gigante, que puede con el tiempo transformarse en una forma más maligna, linfosarcoma, sarcoma reticulocelular, plasmocitoma y endotelioma.

Los síntomas varían por demás en las distintas formas, siendo verdaderamente

variables, dado que el tejido linfoideo se presenta en cualquier sitio. El diagnóstico preciso sólo puede hacerse por medio del examen microscópico de tejido debidamente fijado y adecuadamente teñido.

El tratamiento debe ser misión conjunta del clínico y del radiólogo, y sólo se ofrecen aquí las indicaciones más sucintas. En general, los casos localizados de paragranuloma de Hodgkin, granuloma de Hodgkin, linfoma de folículos gigantes, y hasta de linfosarcoma y sarcóma reticulocelular pueden ser tratados por la excisión con irradiación postoperatoria según esté indicado. En la enfermedad generalizada, el tratamiento consiste en la irradiación a dosis apropiadas. El sarcoma de Hodgkin es rápidamente letal y la respuesta a la terapéutica es, cuando más, temporal, sobreviniendo la muerte por lo general en un año.

The Nitrogen Mustards: Clinical Use[1]

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ONE UNEXPECTED and beneficial by-product of World War II is a method of chemotherapy that undoubtedly is here to stay, at least for some years. This statement refers to the use of nitrogen mustards as palliative agents for certain types of malignant neoplastic processes. While these agents may be said to have failed to measure up to early hopes for them, they have, nevertheless, in a few types of cancer, become well nigh indispensable because of the prompt palliation which they afford.

HISTORY

When, early in World War II, it became known that the nitrogenous analogues of mustard gas were under consideration as possible warfare agents, the Chemical Warfare Service set about producing them in quantity and studying their effects intensively. It was soon noted that not only are the nitrogen mustards strong vesicants, but that their systemic absorption in animals results in toxic actions in tissues, generally in proportion to the degree of rapidity of cellular growth in those tissues. Particularly subject to damage are the lymphoid tissues of the thymus, spleen, and lymph nodes, the bone marrow, and the intestinal mucosa. Disintegration of lymphocytes may be seen in five hours, and the volume of lymphoid tissue will shrink markedly following toxic doses of nitrogen mustards. These agents, according to Gilman, appear to exert their effects on cells in a manner unlike that of any other chemical agent, but bearing many resemblances to the action of x-rays.

Such observations naturally evoked the suggestion that nitrogen mustards might be useful in the treatment of some cellular neoplastic processes, particularly those of the lymphatic system. Accordingly, during the war, clinical investigation was begun under military secrecy. The first patient was treated late in 1942 at the New Haven Hospital by Lindskog. This patient had an advanced radioresistant lymphosarcoma and, although it now appears that he received too large a dose, yet the regression of his tumors and the symptomatic relief were so striking that they amply justified further trials of nitrogen mustards in tumors of the lymphatics. In the next two years extensive clinical trials were made in Chicago by Jacobson's group, in Salt Lake City by Wintrobe's group, in Boston by Dameshek, in New Haven by L. S. Goodman and Gilman, and in Portland (Oregon) by M. J. Goodman. In the fall of 1944, Memorial Hospital began to take part in this project.

Nothing was openly published concerning the pharmacology and clinical effects of the nitrogen mustards until Gilman and Philips of the Pharmacology Section of the Chemical Warfare Service made their announcement in *Science* in April 1946. Two months later Rhoads, as Chairman of the Committee on Growth of the National Research Council, published in the *Journal of the American Medical Association* an official statement summarizing the therapeutic effects of nitrogen mustards known up to that time, and announcing the availability of the methyl-bis(beta-chloroethyl)amine hydrochloride compound for free distribution to qualified institutions for clinical trial as a drug under further investigation. By now the methyl-bis compound has had wide clinical trial by some 240 different users.

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[1] From the Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York, N. Y. Presented at the Thirty-third Annual Meeting of the Radiological Society of North American, Boston, Mass., Nov. 30–Dec. 5, 1947.

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At Memorial Hospital over 300 patients were treated with nitrogen mustard between October 1944 and December 1947. The lymphoma-leukemia group comprises the largest number of patients, 239. This group includes 102 cases of Hodgkin's disease, 66 of lymphosarcoma, and 65 of leukemia. The rest of the series consists of 48 carcinomas of various kinds, including 33 of the lung, and 16 sarcomas.

Clinical reports have been published within the last fifteen months by Wintrobe *et al.*, ApThomas and Cullumbine of England, and the Memorial Hospital group. There is fairly uniform agreement in these reports as to the value of the nitrogen mustard compounds that were used by the various writers, particularly in relation to the lymphomas and leukemias, and as to their toxic effects. These reports deal for the most part with the methyl-bis and tris compounds. In the past two years at Memorial Hospital, the Chemotherapy Division of the Sloan-Kettering Institute has been making an intensive study of numerous congeners in the mustard series in an effort to find compounds that may be more effective and less toxic than those now in use. So far we are not convinced that any have been shown to be superior to methyl-bis(beta-chlorethyl)amine hydrochloride.

In this paper the observations regarding the methyl-bis compound will be summarized.

METHOD OF USE

The methyl-bis compound (HN2) is now available to qualified institutional users packaged in 20 c.c. rubber-stoppered vials, each containing 10 mg. of the substance as a dry powder. Immediately before use, 10 c.c. of sterile physiological saline solution is injected into the vial, and the powder is thus brought into a solution containing 1 mg. of HN2 in each cubic centimeter. The desired dose, which in usual practice has been 0.1 mg. per kg. of the patient's body weight, is then withdrawn into the syringe, and injected intravenously. With careful technic the injection may be made directly from a syringe, or, as preferred by some, the solution may be injected into the rubber tube of an infusion set, through which a small infusion of glucose or saline solution is running rather rapidly. With the syringe technic, it seems advisable to perform the venipuncture with the needle attached to a syringe containing saline solution, then to change to that containing the nitrogen mustard solution, then, after all the nitrogen mustard has been injected, to change back to the syringe containing saline. The two-syringe technic, like the infusion technic, is a precaution for the purpose of minimizing mustard irritation of the vein and overlying subcutaneous tissue.

Dosage: When we began the use of the methyl-bis compound, in October 1944, we had as a guide only a one-day review of 13 cases of Hodgkin's disease that had been treated by Jacobson's group. Our first aim was to determine what this agent could do for advanced cases of Hodgkin's disease that had become refractory to x-ray treatment. These patients were mostly pretty sick, and we tended to be cautious in the dosage of the drug. We therefore began in some cases with only 0.05 mg. per kilogram of body weight, while in some we spaced the doses two or three days apart. Our early results in this type of case were rather disappointing. When we treated some less advanced cases, however, results were better, making it appear worth while to continue the trial of the drug.

As experience grew, we became more familiar with the side actions to be expected and the doses required to produce therapeutic effects. Whereas throughout the country it has been customary to administer 0.1 mg. per kilogram of body weight once a day for four days, we found that it was desirable in some instances to exceed this amount, going on to six or seven or sometimes more such single doses. In some few cases the so-called single dose of 0.1 mg. per kilogram has been given more than once in twenty-four hours. The variation of dosage most commonly used in recent months has been the administration of a so-called double dose, that is, 0.2 mg.

per kilogram, usually on two successive days, followed in some cases by a similar dose on the third, fourth, or fifth day. This doubling of the dose at each injection was based on the observation that it seemed to make the patients no more ill than the single dose, while it had the advantage of shortening the period of hospitalization, cutting in half the number of systemic reactions in any given case, and decreasing the number of venipunctures and hence the risk of chemical phlebitis or an accidental perivenous inflammatory reaction.

Dosage is guided largely by the total white cell count. In cases of Hodgkin's disease or lymphosarcoma, for example, if the white count is normal or elevated, and other circumstances are favorable, it is felt usually that it is safe to give three double doses, a total of 0.6 mg. per kilogram of body weight, and that a considerable leukopenia should be expected to follow within a few days to a week as a measure of adequate dosage.

Repetition of Treatment: In some cases a full course of treatment may be repeated in a month or two. In other cases either the continued effects of the disease or the prolonged effects of the previous administration of nitrogen mustard have held the total white cell count at a low level, so that one would not dare to give another full course. In such instances only one dose of 0.2 mg. per kilogram or two or three doses of 0.1 mg. per kilogram may be decided upon as the maximum safe amount.

Both Jacobson and Wintrobe have reported on maintenance therapy of certain cases, consisting in administration of a total of 0.2 to 0.3 mg. per kilogram in divided doses every few weeks. At Memorial Hospital we have not tested this plan extensively. In general, we have awaited signs and symptoms of beginning relapse before subjecting the patient to another course of the drug.

TOXIC EFFECTS

Toxic effects are both local, at the site of injection, and general, the latter being chiefly gastro-intestinal and hematologic. Some of the congeners of HN2 have produced cerebral toxic effects, but these are practically never seen with therapeutic doses of HN2.

Great care must be taken to avoid introduction of even the slightest amount of nitrogen mustard into the tissue outside the vein, since such interstitial injection will cause pain, followed by swelling, induration, and redness, and an area of painful subcutaneous thickening that will last for weeks to months and that may slough. Even with careful technic the vein may become thrombosed. The tris-compound will often cause marked thrombosis. These thromboses are annoying but have so far not given rise to perceptible embolic phenomena. One practical point, of course, is that all venipunctures, for whatever purpose, in a patient who may need to be treated by nitrogen mustard should be done with a view to saving the patency of the veins. In some patients we have simply run out of veins.

Gastro-intestinal toxic effects are mainly nausea and vomiting. Nausea is felt by most patients in from one to several hours following the injection, and about half the patients will retch and vomit. These symptoms may last for several hours, but in nearly all cases the patient is ready to accept another injection by the next day. In a series of daily injections it has been noted that the reaction is most severe following the first injection. In some patients there has been little or apparently no gastro-intestinal disturbance. Diarrhea is uncommon. Pyridoxine hydrochloride injected intravenously—or preferably intramuscularly in order to save the veins—in from ten to thirty minutes following the nitrogen mustard seems to allay the gastric symptoms in some patients. We avoid giving the two drugs simultaneously or administering pyridoxine first, since it has been listed by Gilman as one of the substances with which nitrogen mustard reacts. Since the reaction of nitrogen solution with cells is believed to take place within five minutes, a delay of ten to thirty

minutes before giving pyridoxine should be ample to prevent it from competing with the tissues in reaction to the nitrogen mustard.

Vomiting may naturally be hazardous in a patient with a marked hemorrhagic diathesis. In one case, in a young man who had an aggressive lymphosarcoma, a diffuse purpura of the whole head and neck developed as a result of straining during vomiting after an injection of nitrogen mustard. One patient with acute leukemia died, apparently of intracranial hemorrhage, after vomiting following an initial injection of the drug. Patients who vomit repeatedly for four to seven days may become considerably dehydrated and may require fluid replacement. They may lose a good deal of weight. One striking sequel of a course of nitrogen mustard, particularly in patients who are benefited by a rapid drop of fever and relief from toxic symptoms, is the appearance of an enormous appetite and rapid increase in weight.

Toxic effects on the hematopoietic system are unavoidable with therapeutically effective doses of nitrogen mustard. The white cell count often shows a fall even before completion of the course of injections. In general, a lymphopenia is followed rapidly by a granulocytopenia, so that within a week or so the total white count may be down to 1,000 cells per cubic millimeter or less. Usually, when the white cells reach so low a level, penicillin is given parenterally, supposedly as a prophylactic against infection. It seems to be the general experience that very few agranulocytotic lesions develop in patients with these extremely low white cell counts. In from two to four weeks the white count usually shows fair return towards normal, although in some of the more seriously ill patients, with Hodgkin's disease or lymphosarcoma, there has been a prolonged leukopenic effect. In these seriously ill patients particularly, in whom no doubt the marrow is already at a low level of activity, it may appear to be severely depressed by a second course of nitrogen mustard and a prolonged leukopenia may ensue.

The platelets at times seem at first to be somewhat stimulated, but usually they drop below normal levels. The count is often well below 50,000, without much and in some cases without any evidence of bleeding tendency; on the other hand, purpuric spots may sometimes be seen with a platelet level well above 50,000. As regards a drop in red cell and hemoglobin values, these effects may occur rapidly in patients having a severe toxic reaction to nitrogen mustard, but in probably the majority of cases it may be questionable whether the anemia is not rather an expression of the state of the patient's disease prior to nitrogen mustard therapy, plus the effects of loss of nutrition. An increase of reticulocytes in two or three weeks following the series of injections of nitrogen mustard may herald an improvement in the red cell count.

RESULTS

I shall not attempt here to give a detailed analysis of results. However, after over three years of intensive daily experience with the use of nitrogen mustard, and the treatment of over 300 patients, some fairly definite opinions have been formed.

Hodgkin's Disease: One hundred and two patients with Hodgkin's disease have been treated. I now regard nitrogen mustard as an indispensable adjunct for the palliative treatment of this disease, but by no means does it replace x-ray therapy. Two groups of patients are, I believe, still best treated by x-rays without nitrogen mustard: (1) those with the disease confined to one group of nodes, in whom early aggressive irradiation should offer a hope for either cure or very long control (and in some of whom perhaps radical surgery should be employed); (2) those showing beginning spread, but in whom the disease is still relatively regional and without marked constitutional symptoms. In this latter group, x-ray treatment will usually give better results if it is well designed, precisely administered, and adequate in dosage. It is in a third group, in which actual generalization has occurred and constitu-

tional symptoms—fever, night sweats, and itching—have appeared, that nitrogen mustard will find its best use. Even in these cases there is usually a place for x-ray therapy, either in conjunction with the course of nitrogen mustard, or as interim treatment of bulky residual nodal masses or bone lesions. Some of these generalized cases will do so well following a course of nitrogen mustard but at the same time have such low white cell counts as a result of the mustard that x-ray treatment is deferred.

The beneficial effects of nitrogen mustard in Hodgkin's disease are rapid drop in fever, relief of toxic symptoms, and variable shrinkage of granulomatous masses and infiltrates. If the spleen is enlarged, it may shrink measurably. Infiltrations in the lung may nearly disappear. In one case with paraplegia and partial paralysis of the upper extremities, the decrease of neurological signs was as rapid as could be expected with the best results of x-ray therapy over the spinal cord. In some cases pain associated with bone involvement has diminished or disappeared, but healing of osseous lesions, such as may follow local x-ray therapy, has not been obtained with nitrogen mustard. Nor has the itching of Hodgkin's disease been relieved as well as one would hope.

The duration of remissions produced by our usual method of giving nitrogen mustard in a concentrated course and then awaiting signs of relapse has all too often been disappointingly short. This leads to the thought that in Hodgkin's disease, the most favorable condition for treatment by nitrogen mustard, further trial of maintenance therapy by judiciously spaced small doses should be undertaken.

Nevertheless, despite its shortcomings, and even were there no hope of better results than we have had to date, nitrogen mustard has been such a valuable aid in the palliation of generalized Hodgkin's disease that I would not want to do without it.

Now, it may be asked, if nitrogen mustard has such a marked effect on generalized Hodgkin's disease, why not employ it for the earlier cases in conjunction with x-ray therapy, in the hope of superior results? The practical objection at present to this plan is that one is poisoning the entire patient for the sake of an effect on a local process which we know from observation will almost always respond better to local irradiation, and in most cases the leukopenia resulting from the nitrogen mustard would probably contraindicate the delivery of an adequate x-ray dose.

In this connection I suggest a project for future study. As far back as 1932 and 1933 I observed the beneficial effects of low-intensity total body irradiation on some cases of Hodgkin's disease which had previously received local irradiation. These patients did better than was expected, both in symptomatic improvement and in length of the interval before relapse occurred. How this effect is brought about is not known—whether it depends on a direct sterilization of early microscopic foci of the disease, or on some unknown general effect on the body's resistance mechanisms. Perhaps it might be worth while to give a small dose of nitrogen mustard, say 0.1 or 0.2 mg. per kilogram of body weight, to some patients in the early or intermediate stages of Hodgkin's disease a month or two after they have been treated adequately by local irradiation in order to try to determine, over a long period, whether they would do better than would otherwise be expected. This would, of course, be a difficult problem to evaluate statistically.

Lymphosarcoma: Lymphosarcoma, of which 66 cases have been treated, may respond to nitrogen mustard injections with rapid though usually incomplete remissions, but in the more aggressive forms of the disease a rapid relapse is the rule, and continued growth of tumor may be seen despite dangerously large doses. Occasionally the use of nitrogen mustard may be a life-saving procedure when other measures seem contraindicated. An example was a patient treated five months ago, an elderly woman with lymphosarcoma growing diffusely in the side of the neck, fixed

to the larynx and trachea, and extending throughout the region of the thyroid gland and down through the upper thoracic aperture. She was orthopneic and had marked stridorous respirations. The surgeon believed tracheostomy would be useless, as he would have to cut through about an inch of tumor tissue overlying the trachea and it was evident that there would continue to be obstruction well below the level of the operation. X-ray therapy was thought to be useless and probably dangerous: a large dose, to get a quick effect, would probably cause complete obstruction of the airway, and fractionated doses would be so slowly acting that it was believed that death would occur before the obstruction could be relieved. As for nitrogen mustard, it was feared that the patient, who was struggling for every breath, would be in great danger of aspirating vomitus and being asphyxiated. It was decided, however, that this risk seemed less than that of either tracheostomy or irradiation. The overnight effect of one injection of 0.2 mg. per kilogram seemed little short of miraculous. The next morning the patient was evidently out of immediate danger. Further injections of nitrogen mustard were given, and then local x-ray treatment to the neck during the next ten days, with the result that the tumor completely disappeared for several weeks, and the patient's life was temporarily spared.

In some of the less acute or aggressive lymphosarcomas and in some lympholeukosarcomas, large doses have produced remissions of a few months to a year or more.

We wish to try nitrogen mustard more extensively in follicular lymphoma. If, as Gilman states, the action of this drug is similar to that of radiation, the result of its use for follicular lymphoma should be prompt and long lasting remission. Our somewhat mediocre results in a few cases which on biopsy of a peripheral node have been called follicular lymphoma are, I believe, to be explained on the same basis as the not infrequent failure to produce complete and durable remissions in some such cases by means of x-ray therapy, namely, that biopsy of a peripheral node revealing follicular lymphoma may sometimes be misleading, in that much of the disease has progressed to reticulum-cell sarcoma.

Leukemia: Sixty-five patients with leukemia have been treated: 17 with acute leukemia, 1 with monocytic leukemia, 17 with chronic lymphatic leukemia, and 30 with chronic myeloid leukemia. Nitrogen mustard can lower the white cell count and in some cases will reduce the size of the spleen or lymph nodes strikingly, so that the result at first seems about like that produced by x-ray treatment. In general, the remissions in chronic leukemia are of short duration—a month or so—and as a rule the differential count is not much altered In the typical case of chronic myeloid leukemia with the characteristic large spleen, it would seem that, as a rule, a longer remission and one accompanied by greater reduction in the splenomegaly can be produced, initially at least, by x-ray treatment of the spleen. Not often does one see rapid gains in the red cell count and hemoglobin following nitrogen mustard therapy of chronic myeloid leukemia to the degree that these gains are seen following an initial course of x-ray therapy.

In the acute leukemias no great beneficial effect can be reported. Symptomatic and objective relief may be seen but are of very brief duration, and blast forms persist in the blood.

A limited experience with *mycosis fungoides* (4 cases) suggests that the chronic type of case without bulky tumors of the skin may do fairly well, but that in the advanced or aggressive cases, while striking and rapid partial remissions may occur, they will probably be followed by rapid relapses, even in the face of dangerously large toxic doses. We have treated only two cases of *polycythemia vera*. They seem to have responded very favorably. In view of Jacobson's good results, we plan to treat more cases of this disease.

Carcinoma of the Lung: Thirty-three cases of bronchial carcinoma have been treated. The first two such cases showed a

dramatic response. The first patient we ventured to treat had an oat-cell carcinoma, obviously unsuitable for either surgery or irradiation, and was placed on the critical list immediately upon admission, as he was evidently doomed to die within two or three weeks, judging by the rapid course and extent of the disease and the symptoms. Never before in all our experience with anaplastic cancer of the lung in this stage had we witnessed a reversal of the expected rapid downhill course. Relief of symptoms took place within a few days. Shortly afterward a similar case was treated, with a similar result. The effect was by no means curative. In fact, it was difficult to see a great deal of improvement on the x-ray films, except for resorption of pleural exudate in the first case. Subsequently, in other cases of anaplastic lung cancer with enlarged supraclavicular nodes due to metastatic cancer, and in which the disease had not reached the terminal phase, we observed prompt relief of signs and symptoms of mediastinal block and decrease in size of the involved nodes. As a rule, these partial remissions have not lasted more than a few weeks unless million-volt x-ray therapy to the intrathoracic part of the tumor and 250-kv. therapy to the metastatic tumor in the neck nodes have been given following the nitrogen mustard. When that is done, the remission, though still only partial, may be of somewhat longer duration. Nevertheless, as a means of palliation of anaplastic cancer of the lung, this combination of a course of HN2, followed by x-ray therapy, has seemed well worth while. In the more routine types of bronchogenic cancer, it is difficult to say that it has produced any better results than x-ray therapy alone.

Other Types of Cancer: About 15 other carcinomas of various kinds and 16 miscellaneous sarcomas have been treated. Here and there, slight to moderate palliation has been observed.

Summary of Results: To sum up the observed results in over 300 cases treated at Memorial Hospital by nitrogen mustard, the following statements may be made:

1. None of the nitrogen mustards so far used has given any indication of ability to cure any of the types of cancer treated.

2. Palliative results of nitrogen mustard therapy have nevertheless been so marked in certain types of cancer as to make us consider this new therapeutic agent indispensable. These types are: (*a*) cases of generalized Hodgkin's disease with marked constitutional symptoms, often amenable to detoxification within a few days by use of nitrogen mustard; (*b*) advanced cases of lymphosarcoma in which some part of the disease is immediately threatening to life and in which the lesion causing the immediate danger is not amenable to surgery or irradiation; (*c*) the anaplastic carcinomas of the lung.

3. In early and intermediate stages of Hodgkin's disease, in most cases of lymphosarcoma, and in most cases of chronic leukemia, it seems doubtful that nitrogen mustard offers any advantage in general over other methods of treatment, particularly over x-ray therapy, or in fact whether, in general, it is as good an all around agent as x-ray therapy.

4. Since only a few of the hundreds of possible nitrogen mustard compounds have been extensively tried clinically, it may be that other compounds will be found that will be at the same time less toxic and more effective in a broader range of cancers.

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SUMARIO

Las Mostazas del Nitrógeno: Su Empleo Clínico

Más de 300 personas, la mayoría de las cuales padecían de enfermedades del grupo linfoma-leucemia, han sido tratadas en el Hospital Memorial (Nueva York) con una mostaza del nitrógeno: clorhidrato de metilo-bis(cloroetilo-beta) amina. Varióse algo la dosis habitual de 0.1 mg. por kilogramo de peso una vez al día durante cuatro días, consistiendo generalmente la variación en administrar una dosis doble (0.2 mg. por kilogramo de peso) en dos días sucesivos y seguir en algunos casos con una dosis semejante el tercero, cuarto o quinto día. En algunos casos se repitió la serie al cabo de uno o dos meses; en otros no lo permitió el estado del enfermo.

Los efectos de la droga son principalmente gastrointestinales—náuseas y vómitos—y hemáticos—leucopenia pronunciada y por lo general baja de las plaquetas a cifras subnormales.

En vista de los resultados obtenidos, cabe hacer las siguientes declaraciones:

1. Ninguna de las mostazas del nitrógeno utilizadas hasta la fecha ha mostrado la menor capacidad para curar ninguna de las formas de cáncer tratadas.

2. Sin embargo, los resultados paliativos han sido tan decididos en ciertas formas de cáncer que nos hacen considerar esta nueva terapéutica como indispensable. Dichas formas son: (*a*) casos generalizados de enfermedad de Hodgkin con pronunciados síntomas orgánicos, a menudo destoxicables en término de pocos días con la mostaza del nitrógeno; (*b*) casos avanzados de linfosarcoma en los que alguna localización de la dolencia amenaza inmediatamente la vida y en los que la lesion amenazante no puede ser cohibida con la cirugia o la irradiación; (*c*) los carcinomas anaplásicos del pulmón.

3. En los períodos incipiente e intermedio de la enfermedad de Hodgkin, en la mayor parte de los casos de linfosarcoma y en casi todos los casos de leucemia crónica, parece dudoso que la mostaza del nitrógeno ofrezca ventaja alguna, en general, sobre otras técnicas terapéuticas, y en particular sobre la roentgenoterapia, y es más, que sea tan eficaz en conjunto como la última.

The Newer Nitrogen Mustards in the Treatment of Leukemia[1]

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SINCE THE DISCOVERY by Gilman, Goodman, Lindskog, and Dougherty (1) of the chemotherapeutic effect of the nitrogen mustards on lymphosarcoma, and their application to the treatment of Hodgkin's disease by Jacobson (2), these agents have been widely used in the treatment of leukemia and the lymphomas (3–7). Because the effect of the nitrogen mustards originally employed in the therapy of neoplastic disease, although definite, was only palliative, a search for related compounds which might exert a more beneficial and more prolonged effect was instituted. In the studies of cancer chemotherapy at the Sloan-Kettering Institute certain nitrogen mustard derivatives have been shown to be effective in prolonging the survival time of mice with transmitted leukemia (8). One of these derivatives has now been examined extensively for its therapeutic value against leukemia in man, and the results are herewith reported.

This new nitrogen mustard derivative, 1:3 propane diamine N N N′ N′ tetrakis-(2-chloroethyl)dihydrochloride, more commonly known as SK 136, is of about the same order of toxicity as methyl bis(2-chloroethyl)amine hydrochloride, the more widely used nitrogen mustard known as HN2, in that the leukotoxic and LD50 doses were approximately the same in mice and in larger animals. It was noted, however, in rats, that with SK 136 convulsions were produced by smaller multiples of the lethal dose than with HN2.

When given clincally in a dosage of 0.1 mg. per kilogram of body weight daily for four to eight doses, SK 136 usually caused much less nausea and vomiting than did HN2, but a slight degree of dizziness was experienced by most patients. This relative lack of nausea and vomiting seemed to be particularly noticeable with cases of chronic myelogenous leukemia, whereas patients with Hodgkin's disease occasionally had as much or more nausea and vomiting than they did with HN2. The dizziness generally was not severe and disappeared in one to twenty-four hours after injection. An occasional patient complained of nervousness and bad dreams following the injections, but no true hallucinations of toxic psychoses were noted. As with HN2, leukopenia and thrombocytopenia were occasionally noted. In contrast to HN2, in which increase of the amount given in a single injection to 0.2 mg. per kilogram of body weight caused no marked increase in the nausea and vomiting, doubling the dose of SK 136 caused the appearance of nausea and vomiting and severe dizziness.

A closely allied derivative, SK 137, 1:3 propane diamine-2-chloro N N N′ N′ tetrakis (2-chloroethyl) dihydrochloride, in which a chlorine was substituted for a hydrogen in the 2-position of the propane moiety, was also tested clinically. The chemotherapeutic activity of the two drugs appeared to be approximately equal, but the appearance of occasional transient toxic psychoses of twelve to seventy-two hours' duration with SK 137 caused its use to be discontinued. This compound had no advantage over SK 136 to offset the added toxic action.

According to the criteria employed in these and in previous studies for the clinical evaluation of chemotherapeutic agents (9), an ideal response would be as follows: the total leukocyte count would

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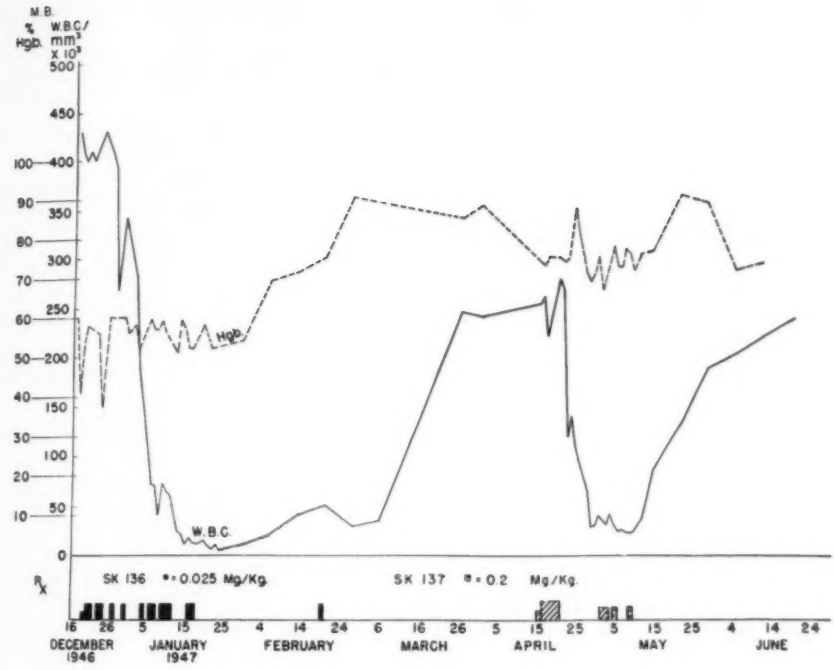

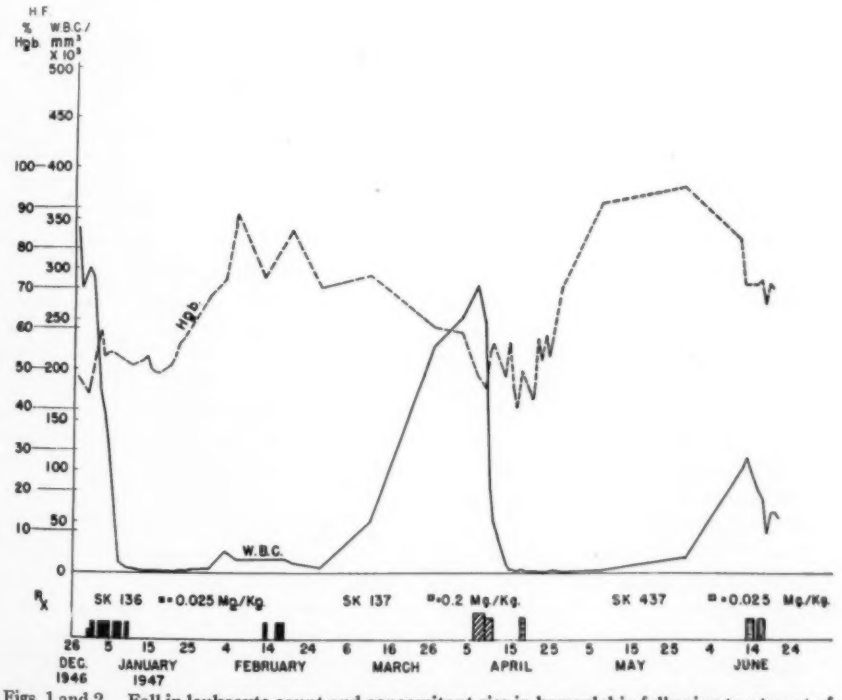

Figs. 1 and 2. Fall in leukocyte count and concomitant rise in hemoglobin following treatment of chronic myelogenous leukemia with SK 136.

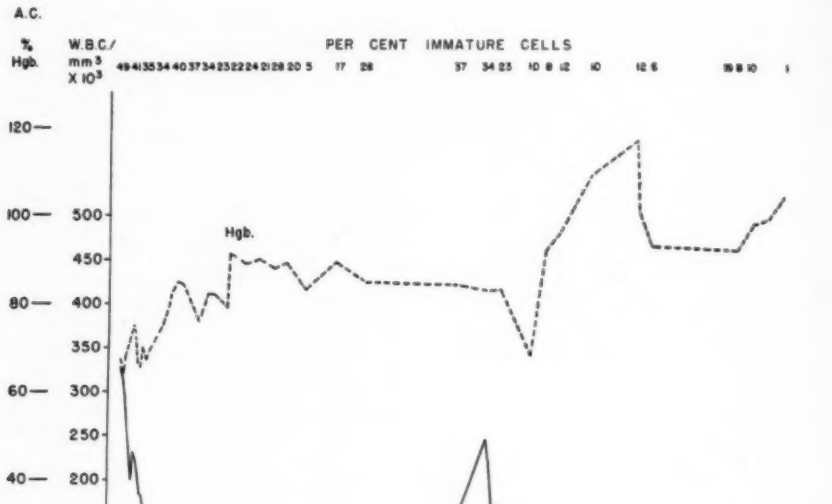

Fig. 3. Control of leukocyte count in chronic myelogenous leukemia by maintenance therapy with SK 136.

fall, the hemoglobin and platelets rise to normal values, and the differential leukocyte count return to normal distribution. The spleen and lymph nodes would decrease to normal size, the fever and hemorrhagic tendency would disappear, and the basal metabolic rate would fall. With the ideal drug such remissions would be permanent or at least repeatable indefinitely.

The shortcomings of SK 136 when judged by these criteria are evident (Table I). Eleven cases of chronic myelogenous leukemia, of which one was terminal, were treated with SK 136. All showed a fall in white count and 9 of the 11 showed a concomitant rise in hemoglobin. There was a marked diminution in the number of abnormal forms in smears of the peripheral blood in 7 cases, but in none of these did the young forms entirely disappear. In 9 patients there was a decrease in the size of the spleen and in 10 a definite subjective improvement. In these patients only a mild degree of dizziness and almost no nausea and vomiting were noted. The average remission of two and a half months was somewhat shorter than would ordinarily be expected from x-ray therapy;

TABLE I: CLINICAL EVALUATION OF SK 136 IN LEUKEMIA

	—Myelogenous—		
	Chronic	Subacute	Acute
Total cases	11	2	19*
Fall in white cell count	11	2	19
Rise in hemoglobin	9	0	3
Improved differential count	7	0	4
Increase in platelets	2	0	3
Decrease in splenomegaly	9	1	10
Decrease in size of nodes	0	..	12
Decrease in bleeding	..	..	3
Subjective improvement	10	1	11
Length of remission in months	1.5–5	1.0	0.5–3

* The results in one case were confused by the almost simultaneous treatment with SK 137 and SK 136.

but the last x-ray-induced remission in 4 of the cases had been no longer than this. Two cases which had shown poor results from x-ray therapy to the spleen, and 3 which had not benefited from Fowler's solution responded to treatment with SK 136. Two cases which are at present on maintenance therapy have been kept in remission, with a white count below 50,000, except for one short relapse each when treatment was discontinued over the summer, for some ten months. One of the patients who initially responded well to SK 136 therapy received little benefit from a similar course of treatment twelve months later, when in a terminal state. This case and one that was terminal at the beginning of therapy indicate that with SK 136, as with radiation, Fowler's solution, urethane, or HN2, there is little beneficial effect at this stage of the disease. Figures 1 and 2 show the fall in leukocyte count and the concomitant rise in hemoglobin following treatment of chronic myelogenous leukemia with SK 136. Figure 3 demonstrates the value of maintenance therapy in control of the white cell count.

In the 19 cases of acute leukemia treated with SK 136, however, the situation was not so satisfactory. All showed a fall in leukocyte count and 3 a rise in hemoglobin and platelets, a differential leukocyte count which returned to normal, and a decrease in bleeding. Eleven of 19 patients showed some evidence of subjective improvement lasting from two weeks to three months coincident with therapy with SK 136; but in only 3 was the remission complete. Inasmuch as these complete remissions occurred in only 3 of 19 cases and could never be completely repeated, we do not feel justified in considering them necessarily as due to the chemotherapeutic action of SK 136. All may well have been spontaneous remissions. Figure 4 shows the fall in leukocyte count without an accompanying rise in hemoglobin which was typical of the response in most cases of acute leukemia. Figure 5 shows a remission of the type that occasionally occurred coincident with SK 136 therapy.

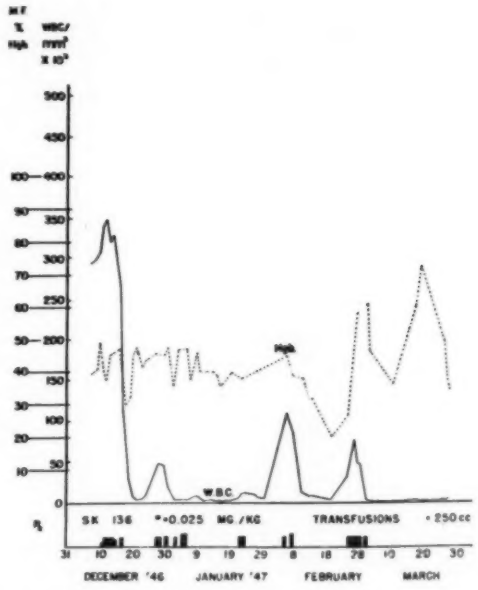

Fig. 4. Fall in leukocyte count without accompanying rise in hemoglobin, a typical response to SK 136 in acute leukemia.

From these studies it would appear that in patients with chronic myelogenous leukemia real, although temporary, remissions were produced with considerable regularity with SK 136. This drug appeared to exert a therapeutic action on the disease similar to that of HN2, radioactive phosphorus, or x-ray therapy. Patients with chronic myelogenous leukemia progress during the course of their disease from a state of sensitivity to treatment to one of resistance. This has occurred with all previously used forms of therapy and appears to be true also of SK 136.

In acute leukemia, however, although a fall in total leukocyte count and a decrease in splenomegaly and lymphadenopathy occurred in most patients, a rise in the hemoglobin, platelets, and the percentage of polymorphonuclear leukocytes was infrequent. The few remissions which did occur could not be repeated, and were therefore presumed to be only coincidental. The therapy of acute leukemia with SK 136, although occasionally promising, has by and large been unsatisfactory.

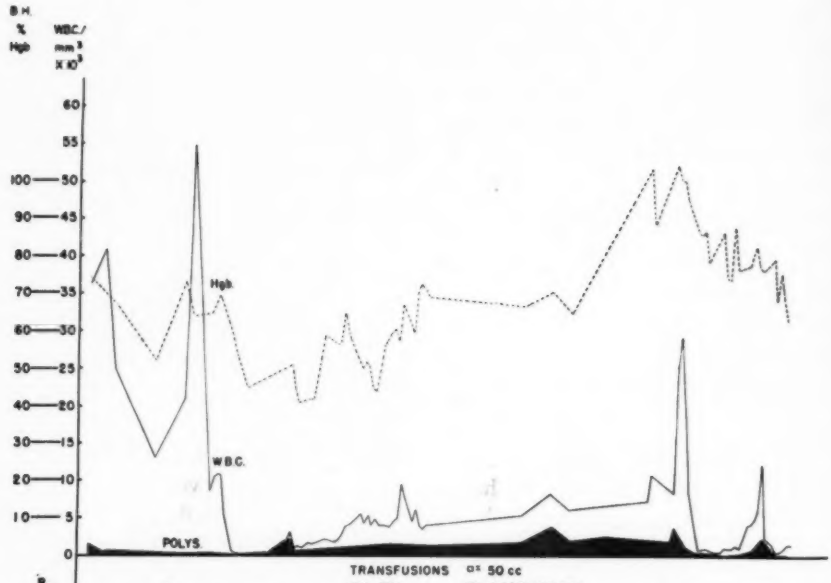

Fig. 5. Acute leukemia: remission of the type occasionally seen coincident with SK 136 therapy.

It is probable that SK 136 has little advantage over HN2 in the therapy of leukemia except in that it appears to be better tolerated by some patients. In an occasional patient with liver and spleen of relatively normal size, SK 136 may be more effective than x-rays. It may also be of some use in cases which no longer respond well to irradiation. In general, however, x-ray therapy is a more versatile and oftentimes a somewhat more effective weapon.

SUMMARY

The therapy of acute leukemia with SK 136 although occasionally promising has by and large been unsatisfactory. In chronic myelogenous leukemia SK 136 produced results similar to HN2, radioactive phosphorus, or x-ray therapy. Although not curative, it seems to be a useful tool in the armamentarium of the clinician. In the majority of cases it offers nothing more than skillfully applied x-ray therapy.

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SUMARIO

Las Nuevas Mostazas del Nitrógeno en el Tratamiento de la Leucemia

En este ensayo se utilizó un nuevo derivado de las mostazas del nitrógeno: biclorhidrato de 1:3 propano diamino N N N′ N′ tetrakis (2 cloroetilo), conocido más generalmente con el nombre de SK 136. Aunque ocasionalmente prometedora, la terapéutica de la leucemia aguda con la nueva preparación resultó en conjunto poco satisfactoria. En la leucemia mielógena crónica, el SK 136 obtuvo resultados semejantes a los del HN2, el fósforo radioactivo o los rayos X. Aunque no curativo, parece constituir un instrumento útil en el arsenal del clínico. En la mayoría de los casos, no ofrece más que la roentgenoterapia diestramente aplicada.

Otro derivado bastante afín, el biclorhidrato de 1:3 propano diamina 2 cloro N N N′ N′ tetrakis (2 cloroetilo), denominado SK 137, reveló actividad quimioterapéutica igual a la del SK 136, pero manifestó propiedades tóxicas que hicieron abandonar su empleo.

Lymphoma of the Conjunctiva[1]

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WHEN A DISEASE occurs with rarity, the general impression in regard to it may be misleading. Primary episcleral or conjunctival lymphoma falls into this category. Patients with this disease usually consult first an ophthalmologist. The clinical impression of the average ophthalmologist is that this type of conjunctival lesion is of a benign character. This opinion may be due to the great rarity of the lesion, to the lack of repeated biopsy studies, or to the fact that there is insufficient time to observe such cases. It is the purpose of the present inquiry to try to clarify the impression of what these tumors are and what the prospects of the patients who bear them may be.

Lymphoid tissue is widely distributed in ocular tissue. It reacts to inflammatory stimulation by proliferation, especially in the conjunctiva. Lymphocytic infiltration after injury may be a benign type of proliferation as in chronic inflammations, a benign neoplastic change, or a malignant neoplastic proliferation and infiltration. While the inflammatory response is common, the malignant neoplasm of the conjunctiva is rare. Besides the conjunctiva, the lids, orbit, and intracranial organs may be involved. Radiologic literature on the subject (17) has been scanty, and contributions by ophthalmologists are not extensive (2–4, 8–10, 12, 17, 20, 22, 25, 28–30). Detailed reviews of the literature have been made by Shannon and McAndrews (24) in 1932, by Leinfelder and O'Brien (18) and by Ennema (5) in 1935, and by McGavic (19) in 1943. McGavic alone made any attempt to consider the fate of the patient.

The material for the present study was gleaned from approximately 1,600 records of patients with lymphomas of all varieties seen at the Massachusetts General Hospital, the Collis P. Huntington Memorial Hospital, and the Massachusetts Eye and Ear Infirmary. Among these were found 49 instances in which lymphomatous tumors of the extra-ocular orbital adnexa were the presenting complaints. Fourteen, or 0.9 per cent of all the lymphomas seen in these clinics, were conjunctival; 35, or 2.2 per cent, occurred elsewhere in the orbit. It must be borne in mind that this high incidence is probably weighted by the fact that many of the patients were seen in, and referred by, an active, special clinic. In the Lymphoma Clinic at the Massachusetts General Hospital a recent study showed that lymphomatous tumors of the orbital adnexa accounted for 1.7 per cent of a group of 288 patients.

Sugarbaker and Craver (27) found that 1 per cent of extranodal primary lymphomas were in the ocular adnexa and that 1.5 per cent of the patients with generalized lymphoma showed involvement of the eyelids, conjunctiva, or orbital tissues. Such involvement as a complicating factor in patients with leukemia is not infrequent, as is well known (6, 23). McGavic (19) credits lymphomas as accounting for 2.6 per cent of extrabulbar tumors. Rones (21) found 19 lymphomas in 11,500 ocular specimens in the Army Medical Museum; 3, or 0.025 per cent, involved the conjunctiva.

Of approximately 1,500 tumors of the ocular adnexa examined at the Massachusetts Eye and Ear Infirmary, lymphoma of the conjunctiva represented 0.9 per cent, lymphoma of the orbit 2.3 per cent.

Of the 14 patients with proved conjunctival lymphoma constituting the basis

[1] From the Department of Radiology, Massachusetts General Hospital, and the Department of Pathology, Massachusetts Eye and Ear Infirmary, Boston, Mass. Presented at the Thirty-third Annual Meeting of the Radiological Society of North America, Boston, Mass., Nov. 30–Dec. 5, 1947.

TABLE I: LYMPHOMATOUS TUMORS OF CONJUNCTIVA: CORRELATION OF AGE, CYTOLOGY, AND AFTERMATH OF TREATMENT

Case Sex Age	Pathologic Diagnosis, Cell Type	Duration on Admission	Presenting Symptom	Local or Generalized	Treatment	Results: Present Status and Duration Following Treatment
1 F 38	Lymphoma Lymphocytoma	2 mo.	Conjunctival infiltration	L	800 r	Well. Slight conjunctival injection. 1/2 yr.
2 F 70	Lymphoma Lymphocytoma	?	Conjunctival infiltration	L	Excision	Well. 3 1/2 yr.
3 F 68	Lymphosarcoma Lymphocytoma with some reticulum cells	1 yr.	Conjunctival infiltration	L	900 r	Well. 5 1/4 yr.
4 M 60	Lymphoma Lymphocytoma	4 yr.	Conjunctival infiltration	L	600 r	Well. 3 yr.
5 M 53	Lymphosarcoma Lymphoblastoma	1 yr.	Conjunctival infiltration	L	1,000 r	Well. 3 yr.
6 M 58	Lymphosarcoma Lymphocytoma	3 mo.	Conjunctival infiltration	L	1,000 r	Well. Chronic blepharitis. 5 1/2 yr.
7 M 78	Lymphosarcoma Lymphocytic sarcoma	1 mo.	Tumor	L	Radium (58 mg. hr.)	Dead without disease. 2 1/4 yr.
8 M 55	Lymphoma Lymphocytoma and lymphoblastoma	3 mo.	Conjunctival infiltration Generalization	G	600 r	Alive with disease; spleen large. 1/2 yr.
9 M 8	Reticulum cell Reticulum cell	2 wk.	Tumor Orbit involved	G	Exenteration, 300 r, radium++	Lost, with disease. 3/4 yr.
10 F 87	Lymphosarcoma Lymphocytoma; many histiocytes	1 yr.	Tumor Cervical lymph nodes	G	Exenteration	Dead with disease. 1/4 yr.
11 M 70	Lymphosarcoma Lymphocytoma	8 mo.	Tumor Axillary lymph nodes	G	360 Ma min. 6 mg. hr. × 3	Dead with disease. 1 1/4 yr.
12 M 71	Lymphosarcoma Lymphocytoma	4 yr.	Tumor Generalization	G	Excision, x-ray (dose?)	Dead with disease. 1 3/4 yr.
13 M 76	Lymphosarcoma Lymphocytoma	3 mo.	Conjunctival infiltration Generalization	G	600 r	Dead with disease 1/2 yr.
14* M 22	Plasmoma Plasmoma	?	?	L	Excision	Unknown

* Record not available.

for the present discussion (Table I), 5 were female and 9 male. The disease, in this series, occurred commonly among the elderly, almost half of the group being more than seventy years of age, and all save 3 (eight, twenty-two and thirty-eight years, respectively) being over fifty.

HISTOLOGY

The cytology of the lesions was carefully re-examined (Table II), and they were classified along the following lines: (*a*) lymphocytoma; (*b*) lymphoblastoma; (*c*) reticulocytoma; (*d*) Hodgkin's disease; (*e*) plasma-cell. When the local process extends and invades, it is called sarcomatous, and if found in the blood it is classed as lymphatic leukemia. The differing terminology and repetitious titles applied to the lymphomas are complicating. In this study the classification developed by Jackson and Parker (14, 26) and others in the Mallory Institute of Pathology has been adopted (Table III). It meets satisfactorily the test of a permanent histologic classification, namely, usefulness in predicting the clinical course of a disease.

Plasmocytoma is considered as a common name for multiple myeloma, plasmocytoma, and plasma-cell leukemia. Jackson, Parker and Bethea (15) conclude that "multiple myeloma of the plasma-cell type should be classed among the lymphomata."

In this series of 14 lymphomas, 11 are lymphocytomas, one having a considerable number of reticulum cells and another many lymphoblasts, or immature cells; 1 is made up predominantly of reticulum cells;

TABLE II: HISTOLOGIC CRITERIA

	Size	Nucleus	Cytoplasm	Reticulum	Mitosis	Necrosis	Local	Invasive
Lymphoblast	9–20 micra	Larger than mature cell. Border well defined; finely divided chromatin dispersed in nucleus. Single	Narrow; border may stain basically	Not increased	Rare	Rare	Lymphoblastoma	Lymphosarcoma of lymphoblastic type
Lymphocyte	7–10 micra	Dense; massed chromatin	Slight; basic	Not increased	Rare	Rare	Lymphocytoma	If in blood, lymphatic leukemia. Lymphosarcoma of lymphocytic type
Giant follicle lymphoma	Many separate or fused large follicles with active germ centers. Usually limited to lymph nodes and spleen		Germ centers contain young lymphocytes or reticulum cells				Border zone of mature lymphocytes	Half develop Hodgkin's or sarcoma
Reticulum cell	10–20 micra	Ovoid, one side often indented; fine chromatin if mature; coarse in young cells and with nucleolus prominent. Occasionally binuclear	Abundant acid or basic. Some ameboid activity	Increased				Tend to invade veins; spare arteries
Hodgkin's	18–30 micra	Variable cell mixture, lymphocytes, reticulum, and plasma; some eosinophils, polymorphonuclear	Fine reticulated cytoplasm, acid or basic	Increased; fibrosis common		Usual (except paragranuloma type)	Loss of nodal architecture; (limited extent if paragranular)	Paragranuloma not invasive. Granuloma may change over to sarcoma
Sarcoma form is mostly histiocytes	14–20 micra	Always Reed-Sternberg cells, 10–40 micra. Pleomorphic nucleus, sometimes lobulated; multinuclear cells. Chromatin in large clumps and common nucleoli						
Plasmocytoma Usually immature cells are found as well as uninuclear and multinucleated	1–12 micra Polygonal or triangular outline	Round, eccentric, heavy chromatin masses at periphery	Basophilic	Not increased	Common	Rare	May remain local for many years	May involve bones and viscera

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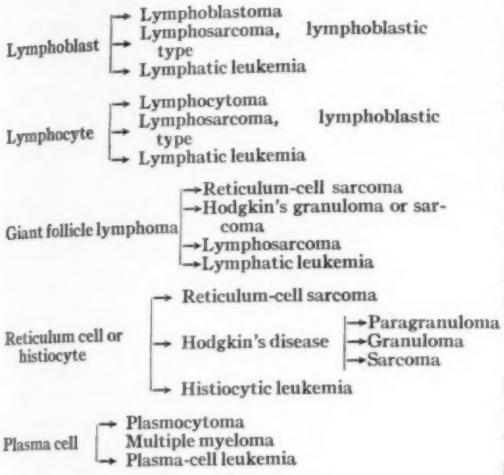
TABLE III: CLASSIFICATION OF LYMPHOMAS BY CELL TYPE*



* From Sparling, Adams, and Parker (26).

another predominantly of lymphoblasts, and 1 predominantly of plasma cells.

CLINICAL DATA

None of the 14 patients is known to have shown an abnormal blood picture at the time of entry, though 6 had evidence of remote disease when they were first seen. Eight, or 57 per cent of the lesions, were invasive and could be called lymphosarcomas. Of the tumors localized to the conjunctiva, 4, or 50 per cent, were infiltrative; none of these has shown evidence of local recurrence or remote manifestations of lymphomatous disease during the period of observation.

Of the 6 cases in which remote disease was evident at the time of first admission, all save 2 were invasive tumors—"lymphosarcomas." All these patients promptly succumbed to their disease with the exception of one with "lymphosarcoma," who was lost with disease within a year, and one with lymphocytic lymphoma, alive but with active disease. This latter patient's blood picture is still essentially normal; his spleen, however, is now greatly enlarged.

TREATMENT

All of the tumors were treated with radium or x-rays save 2, which were excised. In no instance was the x-ray dose needed to produce regression more than 1,000 r. The usual treatment factors in recent years have been 200 kv., 20 cm. object-target distance, 0.25 mm. copper filter. Daily doses of 200 to 300 r have been given, directed onto the conjunctiva, for a total of 600 to 900 r. This has not resulted in any untoward effect upon the eye, immediate or remote. (One eye with an orbital lymphoma, not included in the present study, which received 1,200 r, shows an opacity of the lens five years after treatment.)

Radium treatment has not been used routinely. Excision of the lesion alone, which has been tried only once, in a patient with localized involvement, has not been followed by recurrence in a period of three and a half years.

RESULTS

Table IV demonstrates the status of the 14 patients with regard to freedom from disease. In none of those in whom the lymphoma was localized to the conjunctiva when first seen has there been evidence of local or remote reappearance of disease after treatment. Six have been well for two years or more; 2 with invasive tumors for more than five years. In contrast to these, all of the patients whose conjunctival involvement was part of a generalized lymphoma are dead in less than two years or have uncontrolled disease. The eyes in none, however, are recorded as having shown recurrent involvement.

TABLE IV: TOTAL DURATION OF DISEASE

Years	Number without Disease	Number with Disease	Total
0–1	1	3	4
1–2	0	3	3
2–3	1	0	1
3–4	3	0	3
4–5	0	0	0
Over 5	2	0	2
TOTAL	7	6 (4 dead, 1 lost, and 1 alive with active disease)	13*

*Record on fourteenth case, a plasmoma, not available; status unknown.

As would be expected, those patients in whom the disease was localized have a far better expectancy (7, 11) than do those in whom it was not, and it seems that remissions after treatment of such conjunctival infiltrations may be of considerable duration. Since the disease occurs commonly in the elderly, the period of remission may exceed the expectancy of life. Knowing the vagaries of the lymphomas in general, however, one is probably not warranted in counting apparent freedom from disease as a cure. That lymphoma of the conjunctiva, as elsewhere, may be a peculiarly benign, but not necessarily non-fatal, condition, running a long course even when untreated, is shown by 2 cases in this series, in which the disease had been present in the conjunctiva for four years prior to treatment. One of the two patients is alive and well; the other is dead. McGavic (19) quotes a case in which there was a tumor slowly growing for sixteen years, and Knapp is quoted (19) as having a patient free of disease for two years after expression of the lymphomatous material from the lid by roller forceps alone.

That none of the patients with lymphocytic lymphomas observed has yet shown leukemic changes of the blood is probably fortuitous; that such an event may supervene is well recognized (13, 16, 18, 19). There seems to be no reason to disagree with the many observers who believe that lymphoma of the conjunctiva, like all lymphomas, is a fatal disease if the patient lives long enough. That an unusually long period of remission may be expected if the disease is confined to the conjunctiva is borne out not only by the present group but by the observations of others. Duke-Elder (4) suggests that the use of x-ray or radium may have "happy results if the disease is localized." Verhoeff is quoted (19) as stating that he has never seen primary lymphoma of the conjunctiva do other than remain localized. Four of McGavic's cases did so. Rones (21) had a patient with conjunctival lymphosarcoma who remained well eleven years after radium therapy, and Bedelle (1) a patient with epibulbar lymphoma treated by excision, radium and x-ray, surviving nineteen years, during which time there were two local recurrences but no remote disease developed.

SUMMARY AND CONCLUSION

1. Primary "malignant" lymphomas of the conjunctiva are uncommon tumors, seen rarely by the ophthalmologist and still more rarely by the radiologist. They account for less than 1 per cent of a total group of 1,600 lymphomas.

2. Cytologically they are most frequently lymphocytomas, but may be any of the other varieties of malignant lymphoma; they may or may not be associated with leukemia.

3. The histologic character of the lymphomatous disease seems to have no conclusive bearing upon the prognosis, but patients with localized, non-invading lymphocytic lymphomas seem to do better than others.

4. Lymphoma of the conjunctiva occurs more often in the elderly than in the younger age groups.

5. Lymphomatous tumors of the conjunctiva respond well to x-rays in minimal doses.

6. If the tumors are localized, x-ray treatment or surgical removal is followed by a long period of remission during which remote disease is not manifest.

7. The clinical course of 14 patients with lymphoma of the conjunctiva has been charted; it is interesting because of the survival and/or the result of treatment. In general, it bears out the present clinical impression that the disease may be relatively benign in character in that the patient, if he ever dies from lymphocytic extension, may not do so for many years.

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SUMARIO

Linfoma de la Conjuntiva

Los linfomas "malignos" primarios de la conjuntiva son tumores poco frecuentes, que rara vez ve el oftalmólogo y aun más raramente el radiólogo. En un grupo global de 1,600 linfomas inscritos en tres hospitales, sólo 14 (0.9 por ciento) pertenecían a este tipo. La enfermedad es más común en los grupos de edad más avanzada.

Citológicamente, estos tumores son más a menudo linfocitomas, pero pueden corresponder a cualquiera de las otras variedades del linfoma, y pueden o no asociarse con leucemia. La histología de la afección linfomatosa no guarda al parecer relación terminante con el pronóstico, pero aparentemente lo pasan mejor que los demás los enfermos con linfomas linfocitarios localizados no difusivos.

Los linfomas conjuntivales responden bien a los rayos X a dosis mínimas. Si están localizados, la roentgenoterapia o la extirpación cruenta va seguida de un período prolongado de remisión sin manifestaciones remotas.

La evolución en los 14 enfermos que comprenden la serie actual corrobora, en general, la presente impresión clínica de que la dolencia puede ser relativamente benigna, dado que el sujeto, si es que muere de difusión linfocitaria, tal vez no lo haga por varios años. En ninguno de aquellos en los que el linfoma se hallaba localizado en la conjuntiva al ser observados por primera vez, ha habido signos de recurrencia local o remota posterapéutica. Seis han estado bien por dos años o más, y 2 con tumores difusivos por más de cinco años. En contraposición, todos aquellos en los que la lesión conjuntival formaba parte de un linfoma generalizado murieron en menos de dos años o viven con la enfermedad incohibida. No obstante, en ninguno se menciona que los ojos hayan mostrado invasión recurrente.

Lymphoid Tumors[1]

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UP TO THE PRESENT, our attitude toward the treatment of lymphoid tumors has been one of looking upon the disease as hopeless rather than as curable. This feeling of hopelessness has spread not only to the general practitioner and the laity, but also to the specialist. Recent reports indicate that a different situation exists. A review of these reports and résumé of our own cases have led us to believe that some of these patients may be cured and that many of them may lead a happy and healthy life for a period of five years or more.

It would be less difficult to discuss lymphoid tumors as a group or individually if a uniform histologic classification could be adopted. It would lead the physician to a more accurate prognosis if he could determine whether the disease is localized (unicentric) or generalized (multicentric). Shields Warren (15) has developed a satisfactory histologic classification which is clear, simple, and usually applicable to the clinical findings. It is similar to the outline used by others. It is to be hoped that a universal nomenclature will be developed similar to that used by anatomists.

The histologic classification used in reporting our series is shown in Figure 1. In this classification it is considered that these tumors arise from a reticulum-cell source. From the lymphoid phase of the reticulum cell, lymphosarcoma, lymphocytoma and lymphatic leukemia are derived; from the reticulum side, Hodgkin's disease develops, and from another but unclassified section of the reticulum cell the macrofollicular lymphoma takes its origin. It is apparent from study that this classification agrees with that developed by Jackson and Parker (7) except for their subdivision of the group with Hodgkin's disease. It agrees also with the classification of Bersack (1) except that he further subdivides Hodgkin's disease into lymphoreticuloma, granuloma, and lymphoma. Moore's

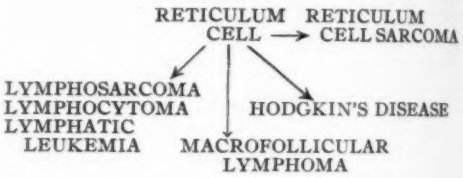

Fig. 1. Histologic classification of lymphoid tumors.

classification (12) is similar to that of Warren, though he has subdivided the malignant lymphomas, and this is largely true of the classification of Gall and Mallory (5), who split malignant lymphomas into stem-celled lymphoma, clasmatocytic (monocytic) lymphoma, lymphoblastic lymphoma, and lymphocytic lymphoma, and subdivide Hodgkin's lymphomas into Hodgkin's sarcoma and Hodgkin's lymphoma. The histologic classification used by Craver (2) resembles that employed by others. He subdivides Hodgkin's disease into atypical, typical, and Hodgkin's sarcoma.

Thus, it is seen that it is almost impossible for one working from the clinical aspect to form an opinion regarding treatment and diagnosis unless he is well acquainted with the histologic material. It is evident that the therapist must depend upon the pathologist for histologic sub-

[1] Presented at the Thirty-third Annual Meeting of the Radiological Society of North America, Boston, Mass. Nov. 30–Dec. 5, 1947.

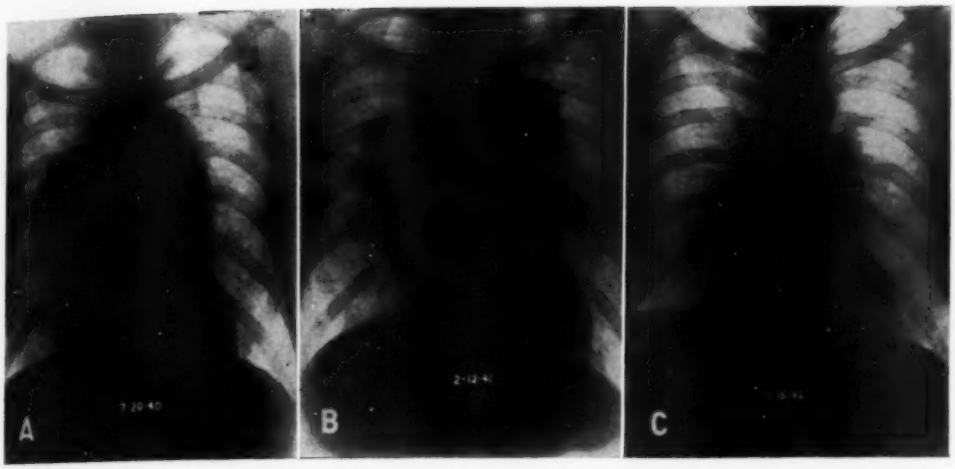

Fig. 2. Mediastinal Hodgkin's disease. A. July 20, 1940 (biopsy of node of neck). B. Feb. 12, 1941, showing growth of tumor in seven months. No treatment given. C. Dec. 15, 1942, twenty-two months after treatment. Patient remains well without evidence of disease to date (Dec. 5, 1947).

classification, but treatment must be carried out on the basis of the clinical findings.

ETIOLOGY

Lymphoid tumors, as classified, apparently are of neoplastic origin and if untreated will invariably result in the death of the patient. It is well known that they respond only to therapy similar to that of other neoplasms. A further breakdown of the histologic study reveals a common source of the tumor in the reticulum cell. The type of lymphoid tumor is the result of the amount of derangement of growth pattern, according to Herbut, Miller, and Erf (6), who have shown in experimental animals and human beings that they can produce changes in the reticulo-endothelial system similar to many lymphoid tumors and can change the apparent course of a lymphoid tumor. Miller, Herbut, and Jones (11) demonstrated the presence of stimulator substances, myelokentric acid (myeloid) and lymphokentric acid (lymphoid), in abnormal amounts in the urine of patients with lymphoid tumors, the amounts depending upon the type of tumor. These substances are also found in the lipids of normal beef livers. Herbut, Miller *et al.* (6, 11) believe that these substances are of fundamental importance in the abnormal processes of blood cell production in the leukemias. For example, an excess of stimulator substances, myeloid and lymphoid, without cell maturation is associated with monocytic leukemia. Both stimulator substances with cell maturation are associated with Hodgkin's disease and when injected into guinea-pigs produce a reaction similar to Hodgkin's disease.

It has undoubtedly been proved by these four workers that the above-mentioned stimulator substances are irritants or carcinogenic agents, capable of producing changes similar to the clinical and pathologic manifestations of lymphoid tumors in human beings.

INCIDENCE

Numerous reviewers have indicated that the incidence of the lymphoid tumors is higher than is generally expected (Tables I and II). Craver (3), in a recent article, said that one out of every 16 persons dying of cancer in the city of New York dies of a tumor in this group, and further that there were 5,009 deaths from this type of lesion between 1940 and 1945 in that city.

Sachs and Seeman (14) have reported that leukemia in the United States has risen continuously since 1920, with an accelerated rate of increase since 1930.

TABLE I: DEATHS FROM CANCER

(Cancer Clinic Cards, Massachusetts)

Site	1946	1945
Stomach	59	68
Breast	198	219
Hodgkin's disease (including lymphoblastoma and lymphosarcoma)	42	48
TOTAL	299	335

TABLE II: TOTAL CASES OF MALIGNANT DISEASE AT PONDVILLE HOSPITAL, WRENTHAM, MASS. 1927–46

Breast		17,003
Lymphoma		364
Giant follicle	10	
Hodgkin's disease	186	
Lymphoma unclassified	74	
Lymphocytoma	2	
Lymphosarcoma	75	
Lymphosarcoma (reticulum-cell type)	9	
Mycosis fungoides	5	
Thymoma	2	
Polymorphous-cell sarcoma	1	

The rise from a rate of 1.9 per 100,000 population in 1920 to 3.7 in 1940 represents an increase of 94.7 per cent in this twenty-year period. Each year since 1940, more than 5,000 persons in the United States have died of the leukemias. The incidence in white persons is more than twice as great as in non-whites. The rate in males is approximately a third greater than that in females.

It is interesting to note that the incidence of Hodgkin's disease is highest between the age of twenty-one and thirty years. Merner and Stenstrom (10) determined this figure from 185 cases proved by biopsy.

CLINICAL FEATURES

The onset of lymphoid tumors is insidious. In approximately 61 per cent of cases, it is first noted as an enlargement of the lymph nodes of the neck. The enlarged nodes frequently follow an upper respiratory infection and subsequently recede only partially or not at all. It is well known that the disease may have its origin in practically any part of the body and may become generalized before the diagnosis is considered, at which time it is impossible to determine whether the lesion was ever unicentric or localized.

If biopsy were carried out in all cases of single lesions of the lymph nodes when they were first noted, the chances of survival would certainly be improved. Records show that approximately sixteen months elapse from the time of onset to the first treatment.

Localized Disease: When the disease is localized, no symptoms are present other than enlarged nodes unless the localized lesions produce pressure or mechanical effects. The blood findings at this time are within normal limits except that occasionally the sedimentation rate may be elevated.

Generalized Disease: The symptoms and findings in generalized disease are as follows: enlarged nodes, weakness, fatigue, loss of weight, and elevated sedimentation rate. The blood findings in leukemia usually are characteristic. A high leukocyte count with increased polymorphonuclear cells is usually seen in Hodgkin's disease. Ten per cent of patients with lymphoid tumors show bone involvement; occasionally there may be generalized pruritus and, less frequently, herpes zoster. Pel-Ebstein fever may be present in the advanced cases. Other symptoms caused by generalized disease depend upon the location of the nodes and the mechanical changes brought about by their presence.

DIFFERENTIAL DIAGNOSIS

Acute cervical adenitis, tuberculous adenitis, infectious mononucleosis, secondary malignant disease, sarcoidosis, and primary malignant lesions in the neck must be differentiated from lymphoid tumors. In cases of mediastinal involvement a differential diagnosis must be made of substernal goiter, aneurysm, neurofibroma, and congenital tumors of the lung and mediastinum. Gastro-intestinal involvement must be distinguished from malignant disease, tuberculosis, regional ileitis, and sarcoidosis.

Methods of Diagnosis: (1) *History:* The onset of the disease is so insidious that no symptoms may be noted other than persistent enlargement of the nodes. With the exception of tuberculosis and sarcoid

disease, no other condition is so chronic. Therefore, if diagnosis is to be made early and treatment instituted, biopsy of these enlarged nodes is a necessity. If constitutional symptoms are present and produced by other than mechanical pressure, the disease is usually beyond the stage of cure or prolonged palliation.

Symptoms of loss of weight, fatigue, bouts of fever, weakness, and pain are all indicative of advanced disease. Abnormal blood changes are evidence of generalization, with the exception of an elevated sedimentation rate, which may be present when the disease is localized.

(2) *Biopsy:* In order that a differential diagnosis may be made, it is important that a biopsy specimen be taken in each instance as soon as the nodes are discovered unless there is good clinical evidence that another process is present. It is important to remember that not all enlarged nodes in cases of Hodgkin's disease reveal evidence of the disease histologically. Occasionally there is evidence only of hyperplasia even though the course of the disease is typical, and in these instances, another biopsy specimen should be taken, and, when possible, several nodes should be removed.

(3) *Trial of Roentgen Therapy:* Roentgen therapy has been used as a method of diagnosis when nodes are not easily accessible for biopsy, as in the mediastinum. No other tumor responds to radiation therapy as rapidly as does the lymphoid tumor, yet one must remember that a scirrhous type of Hodgkin's disease in which there is more than the usual amount of fibrous tissue requires heavier doses of x-rays to bring about shrinkage. Most of the pertinent literature of the past ten years gives results of the use of obliterative irradiation therapy, in which a large enough dose is delivered to destroy the palpable nodes, and an attempt is made to sterilize the field if the tumor is localized. Previously, irradiation treatment had been given only as a palliative procedure, since these tumors usually are radiosensitive and small doses obliterate a large portion of the neoplasm. Palliative irradiation has a place in the treatment of lymphoid tumors, but when the disease is shown by careful physical and clinical examination to be localized, every effort should be made to obliterate every lesion that can be found.

TABLE III: RADIATION TREATMENT OF HODGKIN'S DISEASE

Type	Dosage	Method	Filtration	Time
Localized: curative	2,400 r (tumor); individual size of port	Divided dose	1 mm. Cu and 1 mm. Al	Within three weeks
Generalized: palliative	1,200–1,500 r (air); port not over 250 sq. cm.	Divided dose	1 mm. Cu and 1 mm. Al	As necessary

TREATMENT

It is obvious from a review of our cases, which must be similar to those of other institutions, that most of the time and effort in the treatment of lymphoid tumors are spent on the advanced cases. When it is considered that 50 per cent of patients suffering with this disease are dead within one year following the establishment of a diagnosis, it is realized how many come for treatment far too late. In other forms of malignant disease the case would be considered hopeless and no treatment would be given. It is important, therefore, that we bend our efforts toward the vigorous treatment of those patients who show early manifestations by prompt recognition and diagnosis, with biopsy, and immediate institution of therapy.

Treatment of Localized Disease. (*1*) *Roentgen Therapy* (*Table III*): Irradiation therapy in cases of localized lymphoid tumors must be directed to all palpable nodes and the surrounding tumor bed area, with a total dosage of 2,400 r delivered to the tumor. In many instances several fields must be treated to cover the entire tumor area even though the disease is considered localized. For example, if a patient has a localized lesion on the left side of the neck, 3 to 4 cm. in diameter, and there is no other evidence of disease, a field of at least 10 × 10 cm. should be treated, using 200 kv.p., with copper filtration, half-

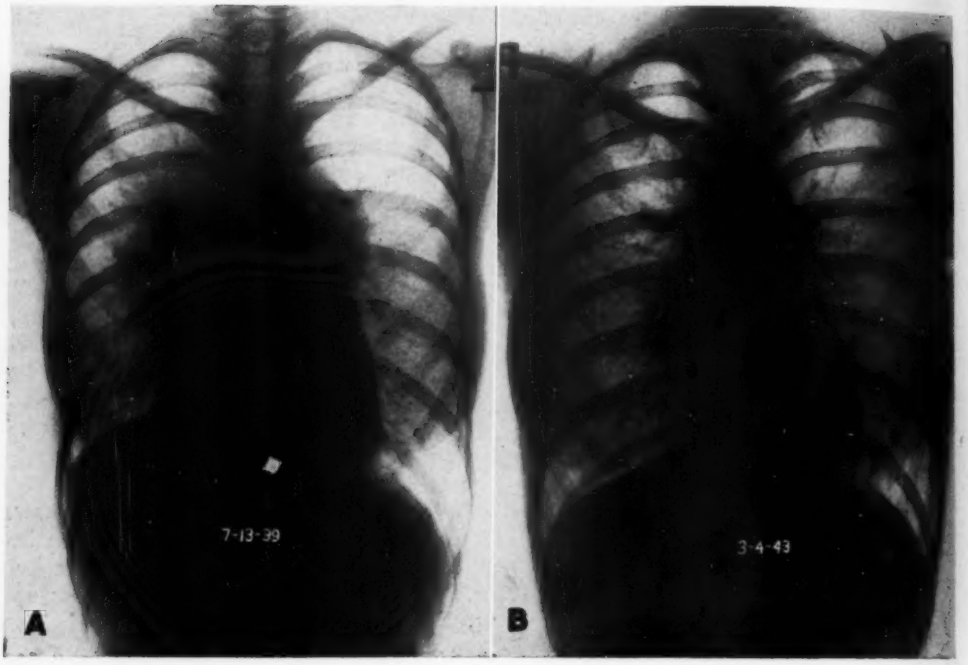

Fig. 3. Mediastinal Hodgkin's disease. A. July 13, 1939 (biopsy of node of neck). B. March 4, 1943, following roentgen treatment (2,400 r) to tumor.

value layer 1.6 mm. Cu, and a total tumor dose of 2400 r.

Since mediastinal involvement may be of the scirrhous type, at least 1,200 to 1,500 r should be delivered to the tumor in the first course or series to establish the diagnosis. Two weeks after treatment roentgenograms should be taken in the same position as were those which showed the primary tumor, and a careful comparison made. If the lesion is found to be radiosensitive and of the lymphoid type, and there is no evidence of generalization, then treatment should be carried out to the fullest extent, as outlined above.

(*2*) *Surgery:* Surgical ablation of localized disease has been used in relatively few instances, because most cases have been considered hopeless once the diagnosis was made, in spite of clinical localization.

Localized disease of the gastro-intestinal tract, including the stomach, terminal ileum, and cecum, is the most amenable to surgical treatment. Marshall (9), in a review of primary lymphoid tumors affecting the stomach in which surgical treatment was given, found a four-year survival rate of 36 per cent in 11 cases. Gall (4) at the Massachusetts General Hospital, reporting on a series of 618 cases, said that some 20 patients of the 250 classified as having Hodgkin's disease, who had surgical extirpation of a localized lesion, lived nearly twice as long as those treated by irradiation, but he does not give the number of patients living five years or longer.

Treatment of Generalized Disease: The treatment of generalized disease in most instances is for palliation only. We do have 3 patients with generalized disease who have lived five years or longer. These cases, however, represent a type of tumor which we cannot explain, for in each instance there was response to very small doses of radiation, yet the histologic characteristics of the lymphoid tissue removed incated that we were dealing with a lymphoid tumor. Since the treatment of generalized disease is designed for palliation, these patients should not receive the heavy doses

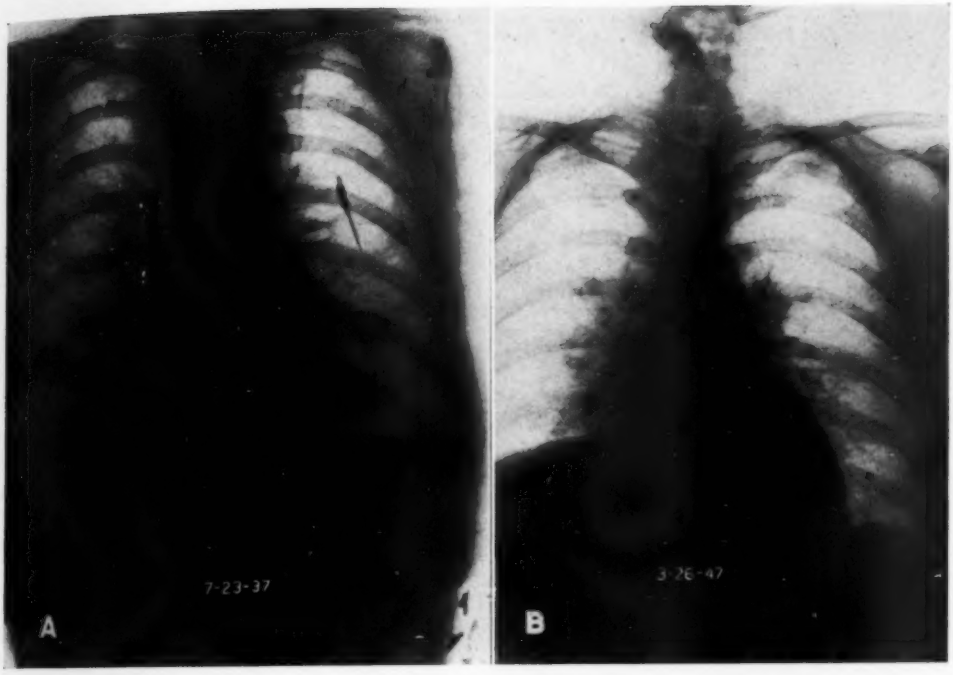

Fig. 4. Mediastinal Hodgkin's disease. A. July 23, 1937 (biopsy of node of neck). B. March 26, 1947, showing no evidence of disease.

of treatment outlined for those with localized disease. We believe 1,200 to 1,550 r, measured in air, is usually sufficient to bring about palliation and shrink the nodes enough to relieve pressure symptoms. In those cases with pruritus, herpes zoster, or bone involvement, special consideration should be given to relief of these symptoms. It is important that radiation treatment not be carried out to the extent that radiation sickness or dermatitis results.

Supportive Treatment: In all cases supportive measures are necessary, especially during the period of treatment. General medical measures only may be required; however, on occasion, transfusions may be indicated in cases of anemia, or intravenous therapy may be employed for radiation sickness.

COMMENT

Jackson and Parker (7) have classified the lymphoid tumors into semi-benign and malignant forms. Without doubt, this fuller histologic classification has some merit, yet the percentage of five-year survivals reported by them (8) is not impressive, except in those patients classified as having paragranuloma, of whom 54 per cent (14 of 26 patients) were alive and well five years or more.

In a review of the cases at the Boston City Hospital, O'Brien (13) reported 116 cases of Hodgkin's disease between 1919 and 1939. Of these, 56 cases were not histologically proved, so that 60 cases were used for his report. The disease had been present for an average of twenty and a half months before roentgen therapy was begun, and the patients lived an average of nineteen months after treatment. Five lived an average of nine years and four months after irradiation, and one lived twenty years.

RESULTS

In a series of 181 cases diagnosed clinically and histologically as lymphoid

TABLE IV: LYMPHOID TUMORS (EXCLUDING LYMPHATIC LEUKEMIA): SURVIVALS 1934–42, INCLUSIVE

Year	Total Cases	1 year	5 years	10 years
1934	8	6	3	3
1935	5	3	3	3
1936	23	11	5	4
1937	26	15	11	7
1938	29	14	6	
1939	31	16	5	
1940	12	6	4	
1941	23	14	10	
1942	24	14	5	
TOTAL	181	99	52	17

NOTE: Of 62 patients seen between 1934 and 1937, 17 (27 per cent) have survived for ten years.

tumors during the years 1934 to 1942, inclusive, 50 patients, or 29 per cent, were living and well at the end of five years and 2 others were living with recurrence of their disease (Table IV). During the period of observation, 30 per cent had recurrent involvement of nodes locally or at a new site, requiring treatment. Thirty-seven, or 71 per cent of the 52 patients living, showed no evidence of recurrence following the initial treatment during the five-year period of observation. The results, then, would indicate that if the disease is adequately treated when localized, a significant number (29 per cent) of patients will obtain a five-year survival.

Of the 62 cases in which treatment was given between 1934 and 1937, inclusive (in which a ten-year follow-up was possible), 17, or 27 per cent, survived ten years or longer. Of this group of 62 patients, 21, or 34 per cent, survived five years or longer. Of the 4 patients who failed to survive the second five-year period, only 2 died of the disease.

Fifty per cent of the 181 patients were dead or lost to follow-up at the end of one year, indicating that palliative therapy for generalized disease may have been effective in relieving symptoms but did not appreciably prolong life.

Forty-one, or 80 per cent, of those who survived five years had Hodgkin's disease, histologically; 8 patients, or 15 per cent, had lymphosarcoma, and 2 patients, or 5 per cent, had lymphocytoma. The results in lymphoid leukemia are not presented.

SUMMARY

Early diagnosis and treatment of lymphoid tumors constitute the only approach to a successful outcome in this disease. Our efforts should be bent toward this end, namely, to establish the diagnosis of the disease while it is still localized and then to deliver an obliterative dose of radiation treatment. The lethal tumor dose in most instances can be fairly adequately attained by giving 2,400 r to the tumor. Fifty (29 per cent) of 181 patients were living and well at the end of a five-year period, and of the 21 patients followed for a ten-year period, 17 remained alive and well.

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SUMARIO

Radioterapia de los Tumores Linfoideos

Si bien la actitud desplegada hacia los tumores linfoideos ha sido pesimista en el pasado, un repaso de la literatura más reciente y el estudio de su propia serie hace creer a los AA. que algunos de esos enfermos pueden curarse y muchos pueden llevar una vida feliz y saludable por cinco años o más.

El diagnóstico y el tratamiento tempranos constituyen la única senda que conduce al éxito, y no debe menospreciarse esfuerzo alguno para establecer el diagnóstico mientras la enfermedad se halla aun localizada y para entregar una dosis obliterante de radiación terapéutica. En la mayor parte de los casos, puede alcanzarse bastante bien la dosis tumor letal aplicando 2,400 r al mismo. Para efecto paliativo, que suele ser todo lo que cabe esperar en la enfermedad generalizada, suelen bastar 1,200 a 1,550 r (al aire) para contraer los ganglios y aliviar los síntomas debidos a la presión.

De una serie de 181 enfermos con tumores linfoideos diagnosticados clínica e histológicamente (la leucemia linfática excluída), 50 (29 por ciento) se hallaban vivos y bien al cabo de un período de cinco años, y de 21 observados durante diez años, 17 permanecían vivos y bien.

DISCUSSION

(Papers by Mixer and Kirschbaum; Jackson; Craver; Burchenal; Schulz and Heath; Hare, Mulry and Sornberger)

Maurice Lenz, M.D. (New York, N. Y.): I congratulate the participants in this Symposium on their interesting contributions and feel it a privilege to discuss their papers.

The demonstration by Drs. Mixer and Kirschbaum that the additive effects of x-rays and methylcholanthrene in producing leukemia are limited to susceptible strains of mice, may be of indirect interest to radiologists. Leukemia occurs more often among radiologists than among other physicians. Exposure to small doses of x-rays over a long period of time is presumably the leukemogenic agent, but, in spite of similar exposure, only some radiologists get leukemia while others do not. Perhaps this is due to an individual genetic susceptibility.

The need for a uniform microscopic classification of lymphomas is evident from this symposium. Dr. Stout, who has classified all of our cases, divides lymphosarcomas into reticulum- and lymphocytic-cell types and giant follicle lymphosarcoma. Among 200 cases receiving roentgen therapy for lymphosarcoma 105 were classified as reticulum-cell lymphosarcoma; 10 per cent of these showed five-year freedom from clinical evidence of lymphosarcoma and 7 per cent ten-year freedom. Corresponding figures for 61 cases designated as lymphocytic lymphosarcoma were 21 per cent and 14 per cent, while among 34 cases of giant follicle type the five-year figure was 32 per cent, dropping to 11 per cent at the end of ten years. Thus, it is evident that while giant follicle lymphosarcoma is more benign in the beginning, it is as lethal as the rest at the end of ten years; reticulum-cell types being the most malignant throughout. The extent of the disease on admission and the clinical acuteness of the process influence prognosis in each of the microscopic groups. Mediastinal and retroperitoneal node cases do badly, perhaps because they are diagnosed relatively late and are extensive when treated. Lymphosarcomas of the stomach, even with regional lymph node involvement, have done well either with x-ray therapy alone or when partially resected and treated with x-rays postoperatively. Lymphosarcoma in children appeared much more malignant than in adults.

Of Dr. Schulz' interesting series of 14 conjunctival lymphosarcomas, only one was of the malignant reticulum-cell type, and this occurred in a child, at an age at which prognosis is notoriously poor. In contrast to his experience, we have followed a patient with a generalized giant follicle lymphosarcoma for fifteen years and he has repeatedly had conjunctival metastases. These disappear promptly after exposure to a few hundred roentgens and sometimes do not recur for years. Another patient, with what appeared as a localized primary lymphocytic-cell lymphosarcoma of the conjunctiva, died a few years later with retroperitoneal lymphosarcoma.

Concerning the claimed superiority of results of

x-ray therapy with preceding surgery over those obtained by x-ray therapy alone, examination of the clinical material may often reveal that earlier cases are referred for combined treatment and more advanced cases for x-ray therapy alone. When cases of similar extent and location are compared with each other, similar results may be expected. Of 8 patients with lymphosarcoma of the stomach in our series, 4 were clinically well at the end of five years. Two of these had partial gastrectomies and two had biopsies only. The bulk of cases of Hodgkin's disease are diagnosed as Hodgkin's granuloma while only a few are grouped as paragranuloma or Hodgkin's sarcoma. Prognosis, therefore, seems to be influenced more by the acuteness and extent of the disease on admission than by its microscopic classification. We believe surgery in Hodgkin's disease and lymphosarcoma should be limited to biopsy; occasionally a resection may be done because of an undiagnosed lymphosarcoma, *e.g.*, in the stomach or small intestine. Yet even in these cases the therapeutic importance of surgery may at times be questioned.

Dr. Hare's tumor dosage roughly corresponds to h at recommended by us. We usually advise a minimum of 2,500 r tumor dose in cases in which a long-term control of the disease is hoped for. Nevertheless, we have seen a number of cases in which tumor doses of 1,000 r were followed by freedom from clinical evidence of lymphosarcoma for a period of five or more years.

As far as the use of nitrogen mustards is concerned, our experience corresponds to that of Dr. Craver. Dr. Gellhorn, who has charge of this treatment at the Presbyterian Hospital, prefers roentgen therapy to nitrogen mustard in cases which are localized and also in reticulum-cell lymphosarcomas. In the latter, results with nitrogen mustard have been very unsatisfactory. In addition to mediastinal, retroperitoneal, or generalized cases of Hodgkin's disease and lymphosarcoma, he has treated 6 cases after extensive radiotherapy. When it became difficult to control the disease by irradiation, nitrogen mustard was given and after a remission of several months the patients appeared once more to become amenable to treatment with x-rays. Such combined treatment may be useful in x-ray refractory cases.

W. Edward Chamberlain, M.D. (Philadelphia, Penna.): I rise to defend Dr. Jackson's point of view with regard to surgery in extremely early, extremely localized lesions. It seems to me, that here there is a definite place for surgery. It is true these are highly selected cases, and they should be so. The minute we depart from the definitely localized, operable case, I agree with Dr. Lenz that we should not use surgery.

I wonder if Dr. Craver has used P^{32} in any cases of oat-cell metastatic carcinoma. We have had some results following its use that are very similar to what he got with nitrogen mustard.

I want to thank Dr. Hare for making the point about the differentiation between cases treated with the hope of cure and those in which only palliation can be expected. I think we radiologists sin more often on that score than on any other. It seems to me that heroic measures in cases that deserve our tender care for palliation produce discomfort and pain that are not justifiable. I also agree with Dr. Hare as to putting the lid on the dosage. I think of late we are still erring in the same direction that we did twenty years ago, like the Indian who thought if one pill per day for a couple of weeks was a good prescription, why not 10 or 20 a day? We radiologists are too apt to think that if a little is good, more is better or, if 1,000 r did not cure all the cases, maybe we would have had better results with 2,000 r.

Dr. Lenz pleased me by reminding us that there are cases that show remarkable results with lower doses. My position is that patients who require heroic measures should have them, but I don't think necessarily we are going to improve our statistics by going on to higher and higher dosages. We have good statistics to show that there are dosages beyond which it does not pay us or our patients to go.

Lateral Intrathoracic Meningocele[1]

MAJ. GENE W. SENGPIEL, M.C., A.U.S., CAPT. FRANCIS F. RUZICKA, M.C., A.U.S., and LT. COL. ELMER A. LODMELL, M.C., U.S.A.

MENINGOCELES not associated with spina bifida occur very rarely. A review of the literature for the years 1920–1946 disclosed reports of only three cases in which the meningocele originated from the lateral aspect of the spine. Pohl (5) in 1933 reported the occurrence of an intrathoracic meningocele in a 47-year-old female patient. Surgery revealed a large cyst containing spinal fluid which communicated with the spinal canal through a 2-cm. opening. Death followed a complicating empyema, and necropsy disclosed some widening of the bony spinal canal at the level of the fourth dorsal vertebra, and a communication with the cyst through a "walnut-sized" opening at the intervertebral foramen between the third and fourth thoracic vertebrae. A synostosis of the third dorsal vertebra was also demonstrated.

Ameuille, Wilmoth, and Kudelski (1) reported a similar case of intrathoracic meningocele in 1940. They described a large lobulated meningocele about 80 mm. in diameter located in the right lower chest posteriorly. Communication with the intraspinal meninges took place by way of a defect that involved "the pedicle and part of the bodies of D-8 and D-9." In addition, there was a moderate kyphos of the lower dorsal region produced by a wedge-shaped deformity of D-9, D-10, and D-11.

Recently, in 1947, Pendergrass, Walker, and Bond (4) reported a case of extraspinal lumbar meningocele in a 32-year-old colored soldier who complained of back pain, headache when bending over and suddenly straightening up, and a mass in the left groin. He gave a history of a crushing injury to the back one year previously. The mass was aspirated, and air injected into the cyst was subsequently observed within the cranium on films of the skull. Myelography with pantopaque demonstrated a communication between the cyst and the subarachnoid space through the twelfth intervertebral foramen. Extraspinal closure of the communication failed, but at a second operation, an intraspinal approach resulted in a cure. The sac itself was not removed. At operation the spinous process of the twelfth dorsal vertebra was found to be poorly developed, and the laminae of the first lumbar vertebra were fused. These authors felt that the previous trauma was of little etiologic significance.

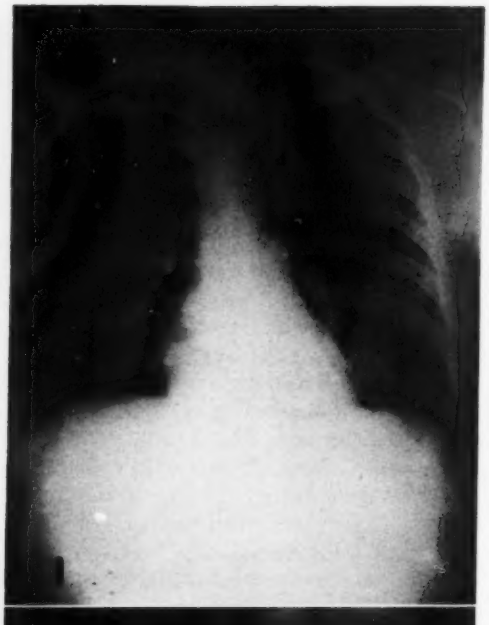
The case of lateral intrathoracic meningocele to be recorded here was discovered incidentally by one of us (G. W. S.) on a routine chest film made prior to separation of the patient from military service.

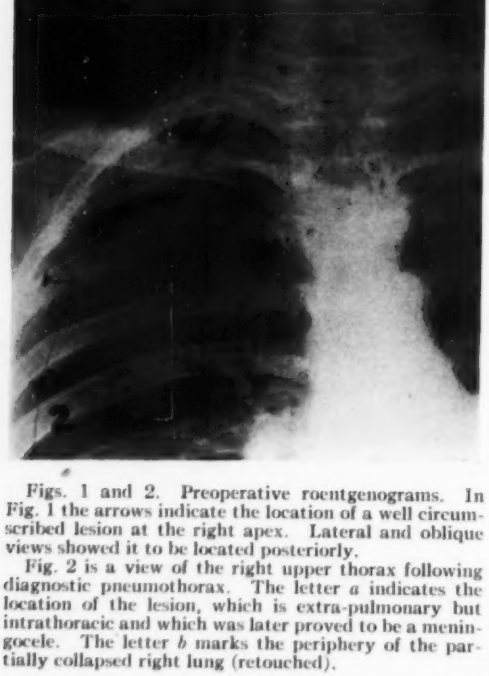
CASE REPORT

In November 1944, a 21-year-old soldier was riding in front of a weapons carrier, which was side-swiped by another vehicle. The patient's right arm was caught between the two vehicles and he promptly lost consciousness. A tourniquet was applied, and upon evacuation, the patient was found to have a compound, comminuted fracture at the junction of the middle and lower thirds of the right humerus. The wound was débrided and a shoulder spica was applied. A complete motor and sensory paralysis developed below the level of the injury. The patient was returned to the United States, and in October 1945, following healing of the fracture, neurolysis of the radial, median, and ulnar nerves was performed. None of the nerves was found to be severed.

In January 1947, re-evaluation revealed only slight return of sensation and no return of motor function. It was felt that a lesion of the nerves might exist at a higher level than at the site of fracture, possibly in the brachial plexus or at the exit of the nerves from the spinal canal. Since further surgery was not considered indicated until after at least a year's observation, the patient was processed for a certificate of disability discharge. The routine

[1] From the Radiological Service, Percy Jones General Hospital, Battle Creek, Mich. Accepted for publication in July 1947.





Figs. 1 and 2. Preoperative roentgenograms. In Fig. 1 the arrows indicate the location of a well circumscribed lesion at the right apex. Lateral and oblique views showed it to be located posteriorly.

Fig. 2 is a view of the right upper thorax following diagnostic pneumothorax. The letter *a* indicates the location of the lesion, which is extra-pulmonary but intrathoracic and which was later proved to be a meningocele. The letter *b* marks the periphery of the partially collapsed right lung (retouched).

separation chest film disclosed a 3-cm. tumefactive lesion high in the right apex posteriorly. There were no symptoms referable to the chest lesion.

The family history is non-contributory. The patient had had an appendectomy in 1944 and a

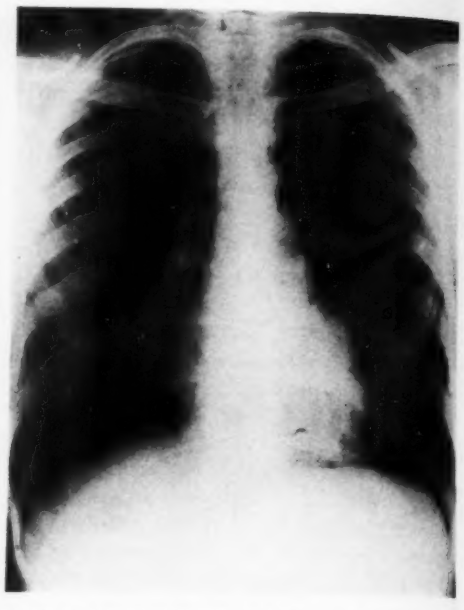


Fig. 3. Chest film made slightly over four years prior to that shown in Fig. 1. There is no evidence of the lesion at the right apex.

herniorrhaphy in 1941. Physical examination was negative except for the motor and sensory paralysis of the right arm. There were no unusual physical findings in the chest. Routine examination of the blood and urine showed nothing abnormal.

On Jan. 9, 1947, x-ray examination of the chest revealed a well circumscribed, rounded, homogeneous mass, 2.5 cm. in diameter, high in the right apex (Fig. 1). On fluoroscopy, the mass showed no pulsation and did not rise on swallowing. No calcification was observed. Anteroposterior and lateral films of the lower cervical and upper dorsal spine revealed no evidence of rib erosion. On Jan. 22, 1947, a diagnostic pneumothorax was performed, 450 c.c. of air being introduced into the right pleural space. Roentgenographically the right lung was seen to have fallen away from the mass and the lesion was shown to be entirely outside the visceral pleura (Fig. 2). The patient's induction film made in 1942 was obtained and revealed no evidence of the lesion described (Fig. 3). The roentgen diagnosis was probable neurofibroma.

On Feb. 24, 1947, thoracic exploration was carried out by Col. E. E. Alling. The lesion was approached posteriorly, with resection of a portion of the second and third ribs. After entering the pleural cavity, the surgeon stated: "... we could feel a mass superiorly that seemed to come from between the first and second ribs at about the costal-transverse process junction. The tumor was then approached extrapleurally between the first and second ribs.

The mass was about 3 cm. in diameter, collapsed very easily on pressure, and refilled when the pressure was released. Since it did not appear to contain blood, a needle was inserted into the cavity and what appeared to be spinal fluid was withdrawn. It was thought impossible and unnecessary to resect this meningocele, which appeared to be connected with the first dorsal nerve, since it is asymptomatic and the patient has probably had it all his life." The fluid aspirated from the cyst, according to the laboratory report, was of clear appearance, containing 37 red blood cells and 3 white blood cells, of which all were lymphocytes. The globulin test was negative. Total protein was reported as 34 mg., and there was no growth on culture. The observations were considered compatible with spinal fluid. The surgeon felt that he was dealing with a meningocele which communicated with the spinal canal between the first and second dorsal vertebrae.

Convalescence was uneventful. To confirm the diagnosis, the patient was returned to the x-ray department on March 14, 1947, and a needle was introduced directly into the meningocele through the posterior chest wall. Three cubic centimeters of pantopaque were then injected into the cyst, and upon turning the patient under fluoroscopic control, the contrast medium was seen to enter the spinal canal very promptly through a communication between the first and second thoracic vertebrae on the right (Fig. 4). Films of the lumbar spine upon completion of the examination revealed the presence of contrast medium in the sacral canal.

On April 17 the patient was again observed fluoroscopically and at this time all the contrast medum had been evacuated from the cyst and lay pooled in the caudal sac. However, upon manipulation, similar to that used in high thoracic myelography, the residual pantopaque readily entered the lateral meningocele. The communication was demonstrated to be through the foramen between the first and second thoracic vertebrae (Figs. 5 and 6). Stereo oblique films disclosed a slight increase in the size of this foramen as compared with the one above and below, and underdevelopment of the right lamina of the first thoracic vertebra. The patient was discharged following the last examination to a Veterans Facility for further observation.

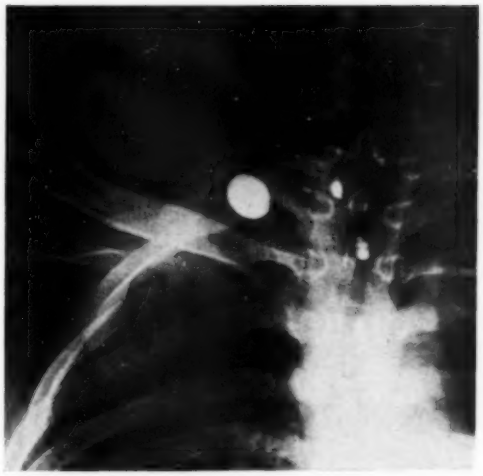


Fig. 4. Film showing pantopaque within the meningocele at the right apex. Injection was made by needle directly into the meningocele through the chest wall. Several groups of conglomerate globules can be seen in the dorsal subarachnoid space. Note surgical resection of proximal ends of 2d and 3d ribs.

DISCUSSION

The consensus of opinion points to the presence of a skeletal defect, usually in the posterior neural arch of the spinal canal, as the primary lesion in the development of a meningocele. Uncommonly a rachischisis occurs in the anterior portion of the vertebral column associated with an anterior meningocele. In each of the three cases of lateral meningocele reported in the literature, some form of congenital anomaly or defect was described in an adjacent segment of the spine. In the present case, the skeletal defect is minimal. The intervertebral foramen at the site of communication appears slightly larger than normal and larger than either the one above or the one below. The width (superior-inferior dimension) of the right lamina of the first thoracic vertebra measures 3–4 mm. less than the lamina of the second thoracic vertebra and is equal to that of the 7th cervical vertebra. Fluoroscopy definitely proved the site of communication between the intrathoracic meningocele and the spinal subarachnoid space to be at the intervertebral foramen between D-1 and D-2.

The skeletal defect appears to play the role of a necessary concomitant in the development of a meningocele. That it is not the only factor is evidenced by the frequent occurrence of spina bifida without associated protrusion of the meninges. In consideration of other factors which may play a part in the production of meningocele, the embryology of the meninges commands attention. The peripheral nerves arise

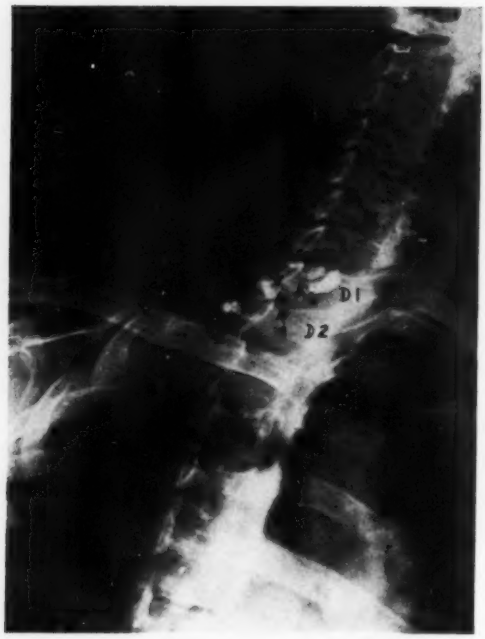


Fig. 5. Left posterior oblique view of cervical and upper thoracic spine, showing right intervertebral foramina. Globules of pantopaque are demonstrated in the meningocele (lateral to spine at right apex), in the dorsal subarachnoid space, and in the communication between the two. The letter *a* indicates the enlarged intervertebral foramen on the right between the first and second thoracic vertebrae, which are marked "D-1" and "D-2," respectively. The letter *b* points out the right lamina of D-1, which is the same in width as the lamina of C-7 and considerably smaller than that of D-2. The letter *c* indicates the resected ends of the second and third ribs.

Fig. 6. Spot film (oblique) of spine at the level of the lesion (same view as Fig. 5). The letter *a* indicates the intervertebral foramen between D-1 and D-2; *b* marks the right lamina of D-1. Note pantopaque in meningocele (lateral to spine at right apex), and also at the intervertebral foramen and in the dorsal subarachnoid space.

from the primitive spinal cord and proceed laterally as the myotomes develop. The dura mater may be recognized as a distinct structure as early as the eighth week in fetal life (2). When fully developed, the dura forms a covering for the spinal cord, and extensions form the nerve sheaths which surround the peripheral nerves in their course through the foramina (3). The fibers in the nerve sheaths arising from the dura normally blend with those of the epineurium of the peripheral nerves at a short distance lateral to the foramina. It is conceivable that the dura might maintain itself as a distinct structure more peripherally than usual, accompanied by the subarachnoid structures, including a subarachnoid space. In the presence of such a patent and elongated dural sheath, one might suppose that a sudden increase in the intraspinal pressure could convert a potential, pre-existing sac into a true meningocele.

Rather than a potential cavity, the common meningocele associated with spina bifida usually presents a sac which fills with spinal fluid during development and exists essentially as a part of the cerebrospinal system. In the present case, however, an earlier chest film, made in 1942, failed to reveal any evidence of the lesion. One must therefore explain the filling of this potential sac which had presumably existed since birth. Coughing, sneezing, straining at stool, etc., are known to cause increased intrathoracic and intra-abdominal pressure, which in turn, by increasing venous pressure, may result in a marked increase in the cerebrospinal fluid pressure. In coughing, for example, the intrathoracic pressure is suddenly greatly increased and is released just as suddenly. The pressure may vary from 100 mm. mercury to 0 mm.

or less during and immediately following coughing or sneezing. The intraspinal pressure does not rise simultaneously with the rise in intrathoracic pressure because of a necessary short interval for transmission of the pressure through the venous system. Because of this brief lag, a situation exists where the cerebrospinal fluid pressure may be considerably elevated, while the intrathoracic pressure is low or even in a negative phase. It is conceivable that during this period, a potential sac might be filled with cerebrospinal fluid in one episode or as the result of repeated episodes of variance between the intrathoracic and the intraspinal pressure. It is not known when the actual filling of the potential sac in the case reported occurred Whether a sudden increase of intraspinal pressure was associated with the trauma this soldier received cannot be determined. It seems entirely illogical to explain the formation of the meningocele on the basis of the direct trauma suffered to the right arm at the time of the accident. Whether the cyst was capable of emptying and refilling itself is also questionable. In a three-month period of observation, it was always present and of the same size.

Regardless of the etiology, this entity adds another condition to the already long list of lesions to be considered in the differential diagnosis of solitary, rounded, well circumscribed lesions appearing in the chest. The importance of a diagnostic pneumothorax is again demonstrated. In this case it easily excluded the possibility of a primary tumor within the pulmonary parenchyma or of an inflammatory process in the lung itself. In retrospect, had the nature of this condition been realized at the onset, the diagnosis could have been established easily by the usual myelographic procedures with pantopaque, thus avoiding the necessity of operation. Even after a period of several weeks, the residual oil was easily made to flow into the meningocele through its opening at the intervertebral foramen. While the lesion may be asymptomatic, as it was in this case, at times the differentiation from an early malignant tumor might be most important.

SUMMARY

1. A case of lateral intrathoracic meningocele has been reported.
2. The literature has been reviewed and the rarity of the condition established.
3. The association of congenital defects in the spine and a possible etiologic mechanism are briefly discussed.
4. While the lesion may be asymptomatic, it assumes importance in the differential diagnosis of serious chest lesions.

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SUMARIO

Meningocele Intratorácico Lateral

Al comunicar un caso de meningocele intratorácico lateral, señálase que sólo se han encontrado tres casos semejantes en la literatura de 1920 a 1946. El enfermo era un soldado, y el meningocele, tomado primero por neurofibroma, fué descubierto en una radiografia torácica de las corrientes, ejecutada antes de dar de baja al individuo por otra incapacidad. La operación en busca del presunto neurofibroma condujo al diagnóstico, que fué confirmado por el subsiguiente examen roentgenológico con pantopaco. La comunicación con el conducto raquídeo era a través del agujero

entre la primera y la segunda vértebra dorsales. La única deformación observable en el esqueleto consistió en un ligero aumento del tamaño del agujero, comparado con el de más arriba y el de más abajo, y atrofia de la lámina derecha de la primera vértebra dorsal. El re-examen de una película torácica tomada previamente no reveló signos de la lesión, y se supone que existió en forma de saco potencial desde el nacimiento, pero no cabe determinar cuándo se llenó realmente con líquido cefalorraquídeo y cuál fué el mecanismo causante.

Aunque un meningocele de ese género puede ser asintomático, reviste importancia para la diferenciación de las lesiones torácicas descubiertas por la radiografía. En este caso, un neumotórax diagnóstico ejecutado antes de la operación excluyó la existencia de un tumor o proceso inflamatorio primario en el pulmón mismo.

Roentgen Manifestations in Hodgkin's Disease of Retroperitoneal Lymph Nodes[1]

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THE ESTABLISHMENT of the presence of involved retroperitoneal lymph nodes in cases of known Hodgkin's disease is not attended with too great difficulty. Desjardins, Lenz, and others have stressed the essential symptoms and findings indicating this possibility, as well as the need for early treatment to this area. Cohen was able to show the presence of a retroperitoneal mass in an established case of Hodgkin's disease by the anterior displacement of a calcified abdominal aorta. The aorta resumed its normal position after radiation therapy to the mass. Weyrauch states that enlarged peri-aortic lymph nodes, by pressure upon the region of the hilum of the kidney, will produce vertical torsion of that organ. He cites a case in which the kidney was displaced laterally and its pelvis rotated in ventral position, as a result of metastatic lymph nodes in the peri-aortic region. An instance of such bilateral symmetrical rotation, caused by a large retroperitoneal mass of lymph nodes situated in the mid-line, was reported by Van Zwaluwenburg and Pascucci.

Desjardins found that in a great majority of cases in which the peri-aortic lymph nodes are affected by Hodgkin's disease, roentgen examination of the gastro-intestinal tract does not yield any evidence of abnormality. Sometimes, however, local abnormality of contour may be found in the stomach or in the small or large intestine. Usually the defect is not constant in outline and is caused by extrinsic pressure.

Craver and Herrmann, discussing abdominal lymphogranulomatosis, state that the initial symptom in the extrinsic gastro-intestinal type of the disease is in most cases abdominal pain or epigastric distress. In carrying out a gastro-intestinal roentgen study in 33 patients of this group, these authors noted that in over 50 per cent no abnormality was revealed. Positive roentgen findings were demonstrable in 14 cases, in only 2 of which was displacement of stomach or duodenum manifested.

It is in cases presenting an obscure diagnostic problem, where Hodgkin's disease of the retroperitoneal lymph nodes may be a possibility and where the institution of appropriate therapy may be unduly delayed until definite proof of its existence has been obtained, that every aid to the establishment of this diagnosis is most welcome. The following case is presented to illustrate this point.

CASE REPORT

A white male, aged 54, was admitted to the hospital because of weakness, "run-down" condition, and loss of 20 pounds in the past four weeks. The illness had started three months earlier, with a hacking, non-productive cough. Upon visiting a physician, the patient was told that he had a high fever. He had never had pain in the chest or elsewhere, but he did have night sweats and continuous fever. Recently he had noticed some shortness of breath. There were no gastro-intestinal symptoms.

The patient appeared moderately well developed, in no particular discomfort and with no evidence of any great loss of weight. The skin was moist and warm. No lymphadenopathy was made out, and the spleen was not palpable. The remainder of the findings were also normal except for a rapid pulse (100–110). During the stay in the hospital, the temperature ranged from 98° to 103°, usually rising in the late afternoon. Hemoglobin was 9.0 gm. and the white cell count ranged from 7,000 to 15,000, with 80 to 90 per cent polymorphonuclears and 1 to 4 per cent monocytes.

[1] From the Radiological Service, Veterans Administration Hospital, Richmond, Va. Published with permission of the Chief Medical Director, Department of Medicine and Surgery, Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author. Accepted for publication in July 1947.

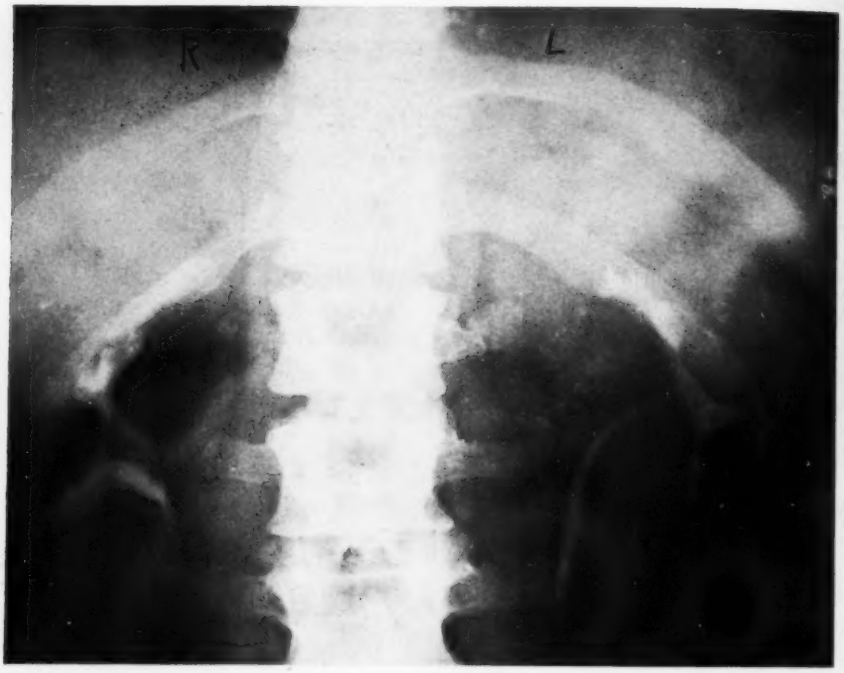

Fig. 1. Roentgenogram showing evidence of a pressure defect on the pelvis of the left kidney. The kidney itself is displaced laterally and is rotated about its axis.

Roentgen examination of the chest, repeated several times, was normal. Intravenous and retrograde urography showed a definite lateral displacement of the left kidney with evidence of extrinsic pressure on the renal pelvis. In addition, the pelvis of the kidney was rotated about its vertical axis (Fig. 1). Barium meal examination (Fig. 2) revealed several smooth concave defects on the superior surface of the duodenal bulb and proximal portion of the descending duodenum. The greater portion of the stomach, the duodenal bulb, and the descending duodenum were moderately displaced anteriorly. Postero-anterior films showed the descending loop of the duodenal arc to be slightly displaced laterally. The possibility of a carcinoma of the head of the pancreas with regional lymph node metastases was considered unlikely because the walls of the duodenum were smooth and regular, and clinical findings did not suggest that possibility. The presence of the multiple smooth defects mentioned above led to the suspicion of the presence of several masses, probably enlarged peri-aortic lymph nodes situated retroperitoneally. This belief was strengthened by the previous observations on the left kidney, as well as by the clinical history. Accordingly, a diagnosis of Hodgkin's disease of retroperitoneal lymph nodes was advanced.

From a clinical study alone no definite diagnosis could be reached, although Hodgkin's disease, among other conditions, was suggested. It was only after roentgen examination of the stomach and duodenum, plus the findings after intravenous urography and retrograde examination of the left kidney, that a definite pathological entity could be considered. Without these findings, one could not proceed with therapy fully convinced as to the underlying nature of the condition. It was then decided to remove one of the lymph nodes in the retroperitoneal area and Dr. Carl C. Bunts, Chief of the Urological Section, excised an enlarged node lying just above the pedicle of the left kidney. The histologic report, by Dr. G. Z. Williams, consultant in pathology, was as follows: "The sections are composed of lymph node-like tissue which is replaced by granulomatous cells including small round, large spindle, and eosinophilic cells. The spindle reticulum cells are large and sarcomatous in character. Numerous Reed-Sternberg giant cells are found. There is considerable fibrosis and much focal necrosis. Diagnosis: Hodgkin's disease."

Nitrogen mustard was administered but produced no clinical improvement. Barium meal examination was repeated in three months, and an increase in size of the retroperitoneal masses was noted (Fig. 2, D). The patient died one month after this last examination and autopsy revealed Hodgkin's disease of the liver, retroperitoneal lymph nodes, and lungs. The inguinal, axillary, and cervical lymph nodes

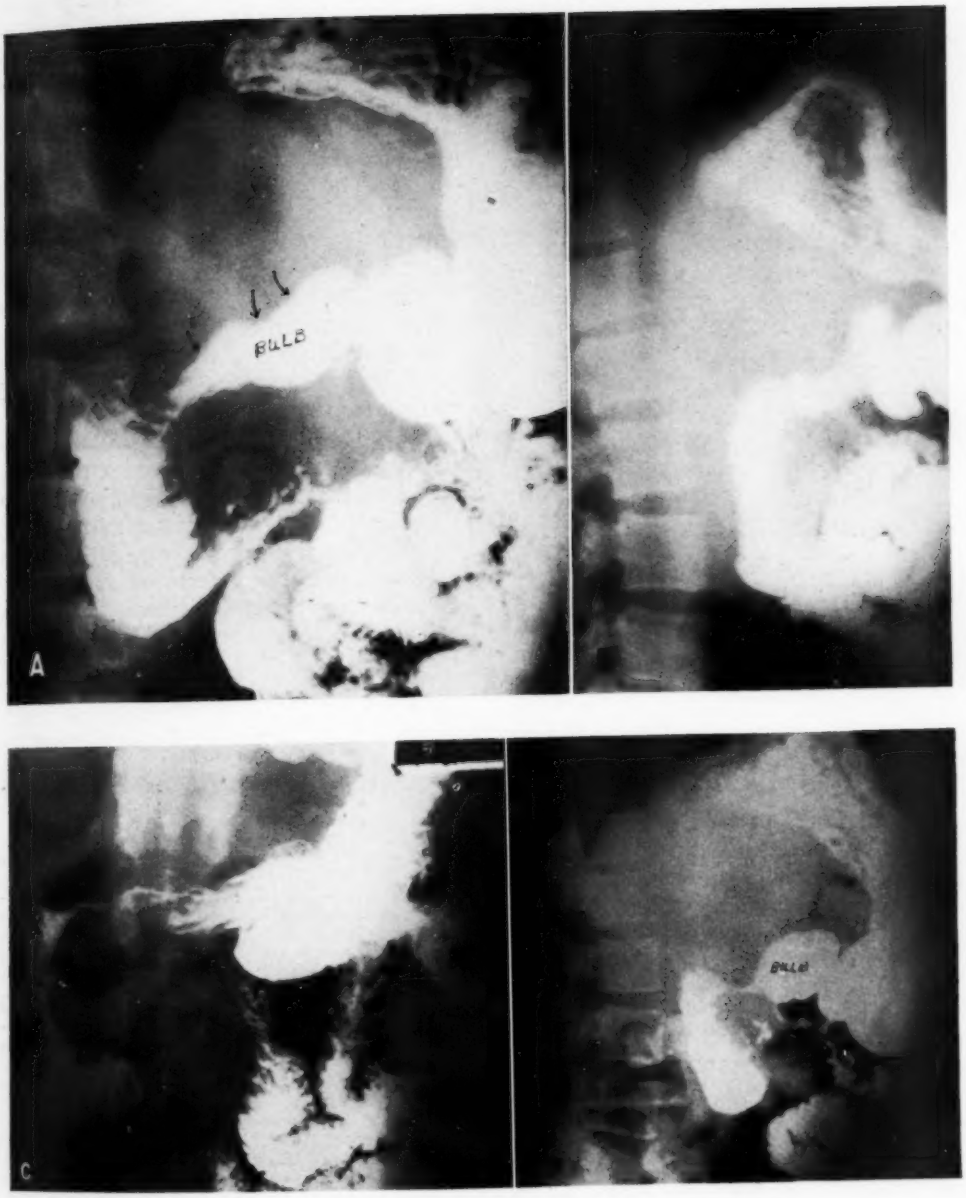

Fig. 2. Barium meal study.

A. Note the smooth, concave defects on the superior surface of the duodenal bulb and proximal portion of the descending duodenum.

B. The bulb and the descending duodenum, as well as the greater portion of the stomach, are displaced anteriorly. In addition, the smooth defects noted in A are again seen.

C. The duodenal arc is widened and the descending portion of the duodenum is displaced laterally but it is not infiltrated by neoplasm.

D. There is now a marked displacement of the entire stomach and duodenal bulb anteriorly. The defect on the proximal portion of the descending duodenum is much more prominent.

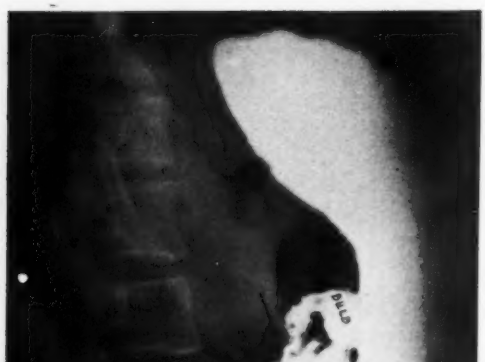

Fig. 3. Sharply outlined smooth defect on the proximal portion of the descending duodenum, with marked anterior displacement of that part.

were also infiltrated by neoplasm. The duodenum was surrounded by a mass of enlarged lymph nodes containing tumor tissue and the posterior wall appeared to be invaded by this mass. The pancreas was firmly matted down but not infiltrated, by enlarged lymph nodes around the celiac and splenic vessels. The spleen was only slightly enlarged.

In another patient, with established Hodgkin's disease in the lungs and peripheral lymph nodes, a pressure defect of the descending duodenum, together with anterior displacement of this part as well as of the duodenal bulb, suggested the presence of involved retroperitoneal lymph nodes (Fig. 3).

SUMMARY

1. A case is reported in which the presence of multiple masses situated retroperitoneally was demonstrated by roentgen examination of the stomach and duodenum. Several smooth, concave pressure defects were noted on the superior surface of the bulb and proximal portion of the descending duodenum. In addition, the major portion of the stomach, the duodenal bulb, and descending duodenum were displaced anteriorly.

2. The left kidney was also shown to be displaced laterally, to exhibit evidence of extrinsic pressure on its pelvis, and to be rotated about its vertical axis.

3. The above findings plus a daily irregular fever of many weeks' duration (with no other established cause) led to the roentgen diagnosis of Hodgkin's disease of the retroperitoneal lymph nodes.

4. The diagnosis was corroborated by histologic examination of one of the lymph nodes situated retroperitoneally. Autopsy confirmed the gross anatomical findings.

5. Also, in a proved case of Hodgkin's disease, pressure defects on and anterior displacement of the duodenum suggested a diagnosis of retroperitoneal lymph node involvement.

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SUMARIO

Manifestación Roentgenológica de la Enfermedad de Hodgkin en los Ganglios Linfáticos Retroperitoneales

Comunícase un caso en el que el examen roentgenológico del estómago y duodeno reveló la presencia de tumefacciones múltiples situadas retroperitonealmente, observándose varias deformaciones por presión, cóncavas y lisas, en la cara superior del bulbo y la parte proximal de la porción descendente del duodeno. Además, hallábanse desplazados hacia adelante la mayor porción del estómago, y el bulbo y la porción descendente del duodeno.

El riñón izquierdo también aparecía desplazado a un lado, revelando signos de presión extrínseca sobre su pelvis, y rotado sobre su eje vertical.

Los hallazgos anteriores, unidos a una fiebre irregular diaria durante muchas semanas, sin ninguna otra causa establecida, condujeron a un diagnóstico roentgenológico de enfermedad de Hodgkin de los ganglios linfáticos retroperitoneales. Así lo corroboró el examen histológico de uno de los ganglios y lo confirmó después la autopsia.

Menciónase también sucintamente un caso establecido de enfermedad de Hodgkin en el cual las deformaciones por presión en, y el desplazamiento hacia adelante del, duodeno sugirieron el diagnóstico de compromiso de los ganglios linfáticos retroperitoneales.

Unusual Friedländer's Bacillus Pneumonia Associated with Septicemia

Case Report and Brief Review of the Literature[1]

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THE PRESENT report was prompted by the observation of a most unusual case of Friedländer's bacillus (*Klebsiella pneumoniae*) pneumonia associated with septicemia due to that organism and characterized by nodular pulmonary densities of a type usually seen with tuberculosis or metastatic neoplasm, but undergoing complete resolution under streptomycin therapy. In view of the efficacy of antibiotic therapy, recognition of similar cases is important. Because they are rare, the basis for their recognition must come from accumulated reports of individual cases or small series.

CASE REPORT

A white male of 63 years was admitted to the New York Hospital on July 10, 1946. Although for one year before admission he had noticed fatigability, a weight loss of 25 pounds, and urinary frequency, his present illness appeared to have begun six weeks prior to admission with a shaking chill. Chills lasting twenty minutes, together with increasing weakness, recurred at weekly intervals until ten days before admission, when three chills in a single day caused the patient to seek medical advice. His local physician discovered diabetes and instituted appropriate therapy, but repeated chills, beginning stupor and disorientation, and temperature elevation to 105° F. led to hospital admission. The only respiratory symptom was slight cough for the two days preceding hospital entry.

Although spiking temperature elevations to 104° F. (40° C.) were to develop soon afterward, the temperature at the time of admission was normal. On physical examination abnormal findings were confined to a general appearance of chronic illness and weight loss and to the chest, which showed dullness and fine râles at the left apex posteriorly and râles at both bases posteriorly, more marked on the left.

Roentgenograms of the chest made shortly after admission showed a well defined and homogeneous spherical or nodular density measuring 2 cm. in diameter in the periphery of the left lung field, in the plane of the first anterior interspace, and a similar density in the interspace below (Fig. 1). Elsewhere there was diffuse accentuation of lung markings without other infiltration. Urine examination showed glycosuria and slight microscopic pyuria. White blood cells numbered 16,500 with 35 per cent band forms and 55 per cent segmented polymorphonuclear neutrophils. Sputum and urine cultures, as well as two blood cultures taken on successive days, were positive for *Klebsiella pneumoniae*.

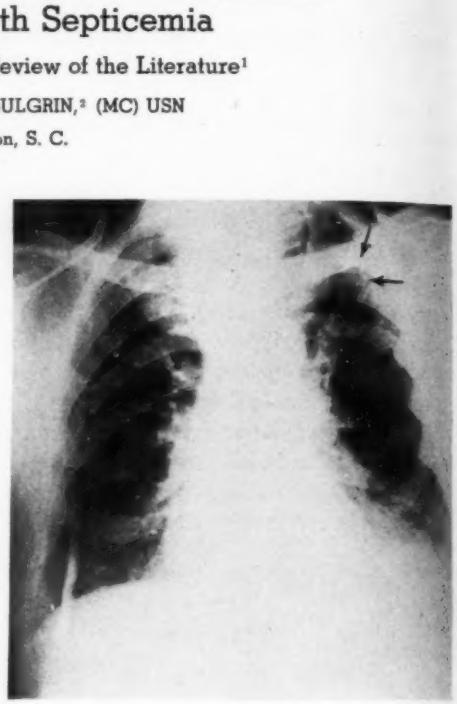

Fig. 1. Initial appearance of nodular parenchymal shadows.

Therapy by sulfadiazine and penicillin, begun with the development of spiking temperature very shortly after admission, was discontinued on the finding of the Friedländer bacillus and replaced by streptomycin in total daily dosage of 3,000,000 units. Under this treatment the temperature fell steadily and the patient had only a low-grade fever by the sixth hospital day. Diabetic control was never

[1] From the Department of Radiology, The New York Hospital. Accepted for publication in July 1947.
[2] Author under instruction. The opinions expressed are those of the author and are not to be considered as reflecting in any way the official views of the Navy Department.

difficult. Streptomycin therapy was stopped but was resumed for a four-day period fairly late in the hospital stay, with control of low-grade fever and sputum, and the patient was discharged afebrile on Aug. 17, 1946. Intensive search for tubercle bacilli or a primary neoplasm had been negative. Although chest films showed clearing of the accentuated lung markings, the nodular parenchymal densities remained at the time of discharge (Fig. 2).

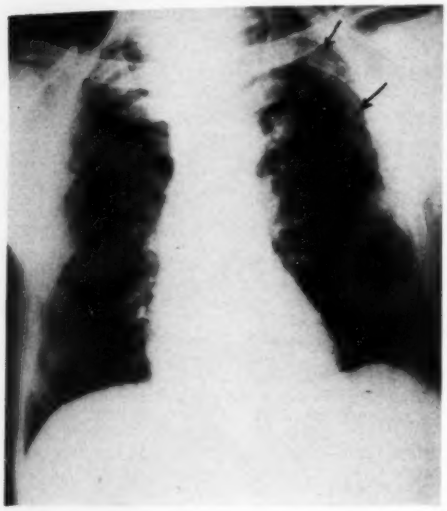

Fig. 2. Persistence of nodular shadows at time of discharge from hospital.

The patient was followed in the Outpatient Department. He gradually ceased coughing, gained weight, and by Oct. 16, 1946, was symptom-free. He has remained so since. On Sept. 17, 1946, roentgenograms showed absence of the nodular shadows, although markings extending from the hilum to their former site remained. On Jan. 27, 1947, chest films were entirely negative (Fig. 3).

DISCUSSION

Friedländer's bacillus pneumonia usually takes the form of a confluent bronchopneumonia, clinically imitating lobar pneumonia of pneumococcal etiology, and showing no preference for any lobe. Large series of acute cases have been reported by Perlman and Bullowa (1), Hyde and Hyde (2), Bullowa, Chess, and Friedman (3), and Solomon (4). The case fatality rate was high prior to chemotherapy and antibiotic therapy. In patients surviving the acute episode, multiple thin-walled abcesses and fibrosis were the outstanding

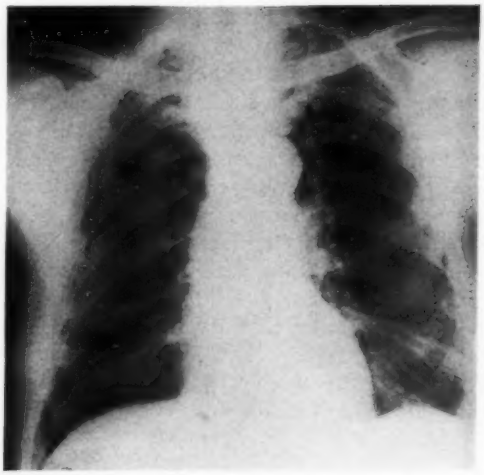

Fig. 3. Complete disappearance of nodular shadows five months after discharge.

manifestations of the chronic form of the disease. Empyema and bronchiectasis have been reported as appearing amid the more characteristic abscesses.

Since reported cases of chronic infection have involved the upper lobes, differentiation from tuberculosis by either clinical or roentgenological means has been difficult, usually being made on bacteriologic grounds. Kornblum (5) enunciated roentgenologic criteria for diagnosis of both acute and chronic cases, Collins and Kornblum (6) published a clinical-roentgenological correlation of a small group of chronic cases, and Solomon (7) collected the largest series of chronic infections.

Among the recorded cases of this condition, acute or chronic, there was none similar to the one here reported. Other cases observed at the New York Hospital, 14 in number, bore no similarity to it, by and large conforming to the usual features of the disease. Search of the literature for similar pneumonia of other etiology was likewise barren of results, with two exceptions: Reimann (8) mentioned the occurrence of nodular or confluent nodular pulmonary infiltrations in tularemia, and assigned to that pneumonia a hematogenous origin, and Sante and Hufford (9) reported a group of 5 cases of unusual pulmonary infection

associated with septicemia. The possible similarity in the latter cases lies in the initial appearance of the pulmonary lesions. There, however, the similarity ends, for in those cases the nodular shadows subsequently assumed an unusual annular form. The patients received chemotherapy, but not antibiotic therapy, and all but one survived. In the survivors the pulmonary manifestations disappeared without a trace except in one instance. Pathologic study of the single fatal case led to presumption of hematogenous origin and the pathogenesis was assigned to bronchial arterial thrombosis with necrosis of bronchial structures.

SUMMARY

A most unusual case of Friedländer's infection of the lung in association with septicemia is presented. It was characterized by nodular pulmonary densities of the type ordinarily attributed to tuberculosis or metastatic neoplasm. These densities disappeared under streptomycin therapy.

No similar cases due to the Friedländer bacillus are reported. The only remotely similar pulmonary lesions of any kind discovered on search of the literature are those mentioned by Reimann in tularemia and a group of unusual pulmonary infections associated with septicemia reported by Sante and Hufford. These instances of questionably similar involvement were assigned hematogenous origin. In the reported case such origin seems not unlikely.

As stated before, in view of the efficacy of antibiotic therapy, recognition of unusual pulmonary lesions associated with septicemia of any kind is important

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SUMARIO

Neumonía Extraña por Bacilo de Friedländer Asociada a Septicemia. Historia Clínica y Breve Reseña de la Literatura

Preséntase un caso extrañísimo de infección pulmonar por bacilo de Friedländer asociada a septicemia, y caracterizado por ganglios pulmonares espesados del tipo que suele imputarse a tuberculosis o metástasis neoplásicas. Dicho espesamiento desapareció con la estreptomicinoterapia.

No se han comunicado casos semejantes debidos al bacilo de Friedländer. Las únicas lesiones pulmonares remotamente similares que revelara una pesquisa de la literatura han sido las mencionadas por Reimann en la tularemia y un grupo de extrañas infecciones pulmonares asociadas a septicemia que comunicaran Sante y Hufford. Estos casos de semejanza dudosa fueron considerados como hematógenos. En el caso descrito ahora, dicho origen no parece improbable.

Según se hace notar, vista la eficacia de la antibioticoterapia, es importante reconocer las lesiones pulmonares extrañas asociadas a septicemia de cualquier género.

Isolated Fracture of the Pisiform Bone

A Case Report[1]

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FRACTURE OF THE pisiform bone without other carpal injury is apparently rather uncommon. The first report of a pisiform fracture, by Guibout (17) in 1847, was in a case complicated by fractures of the navicular, the capitate, and the radius, resulting from a fatal jump from a third-story window. The fracture was proved at necropsy. Jaeger (19), summarizing the literature in 1931, was able to find 11 cases, and reported one of his own. Since then there have been 5 additional reports (6, 8, 11, 12, 24), so that, including the present case, there are on record 18 examples of isolated pisiform fracture. In two instances the reports were in Russian journals which are not available to the author, so that verification of these (12, 24) has not been made.

Schnek (5), in an experience of six years in Böhler's clinic, found 13 pisiform fractures in 437 carpal injuries, but he does not indicate how many of these were isolated fracture of this bone. He states, by way of comparison, that during the same period 669 fractures of the radius and/or ulna were seen. Blumer (3) reports 2 cases of pisiform fracture in 79 carpal injuries from a series of 270,000 examinations for the Swiss compensation insurance system, but these were both accompanied by radial fracture. Destot (10) cites Morgues as giving the incidence as 1 in 61 carpal fractures, but he had not himself seen a case in 500 carpal injuries. Bunnell (7) quotes Snodgrass as reporting 1 case in 170 carpal fractures. Most published reports are, like the present, of single cases. Considering these facts, the incidence might be estimated not to exceed 1 case in 100 fractures of carpal bones exclusively. This apparent rarity, however, may not be truly representative, since the fracture is seldom suspected or looked for, and there is, moreover, a very reasonable reluctance on the part of most physicians to report single cases of a relatively unimportant condition. In addition to fracture, dislocation of the pisiform has been reported, apparently with about the same frequency of occurrence.

The demonstration of the fracture depends on taking an 80° oblique view of the wrist with the dorsum turned back, although in the case here reported, as well as in Jaeger's illustrations, the fracture was readily visible on the palmar projection. The injury must be distinguished from the anomalous bones, the secondary pisiform, the os triangulare, and the separate styloid process of the ulna, but these as a rule lie between the pisiform and the ulna rather than in the pisiform region proper (4).

The pisiform serves as the insertion for the flexor carpi ulnaris and the abductor digiti quinti, and as attachment for the transverse carpal ligament. In some cases, the mechanism seems to have been muscle pull against a forcibly hyperextended hand, with a transverse separation of the bone, while in others, a direct blow on the palmar surface of the wrist over the bone is responsible. Usually the exact mechanism cannot be determined, as was the case in our patient, but the first of those mentioned seems to be the commoner. Hönigschmied (18), in studies on anatomical preparations, noted that in 2 of his experiments the ligaments between the pisiform and triquetrum were torn by extreme radial flexion, but, since he produced no fracture, the element of muscle pull must also come into play. Schnek (27) calls attention to the fact that fractures in the pisiform closely resemble in appearance those in the patella, being either transverse or stellate; the mechanism is presumed to be similar.

[1] Accepted for publication in June 1947.

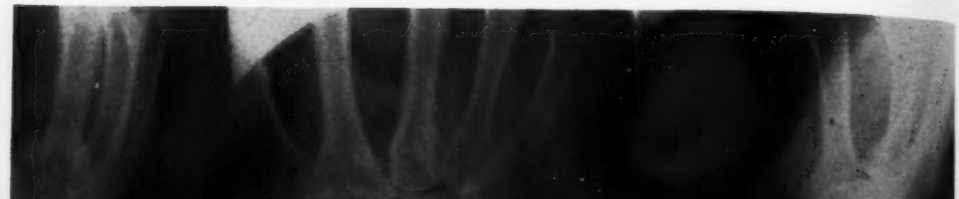

Fig. 1. Left wrist, showing fracture.

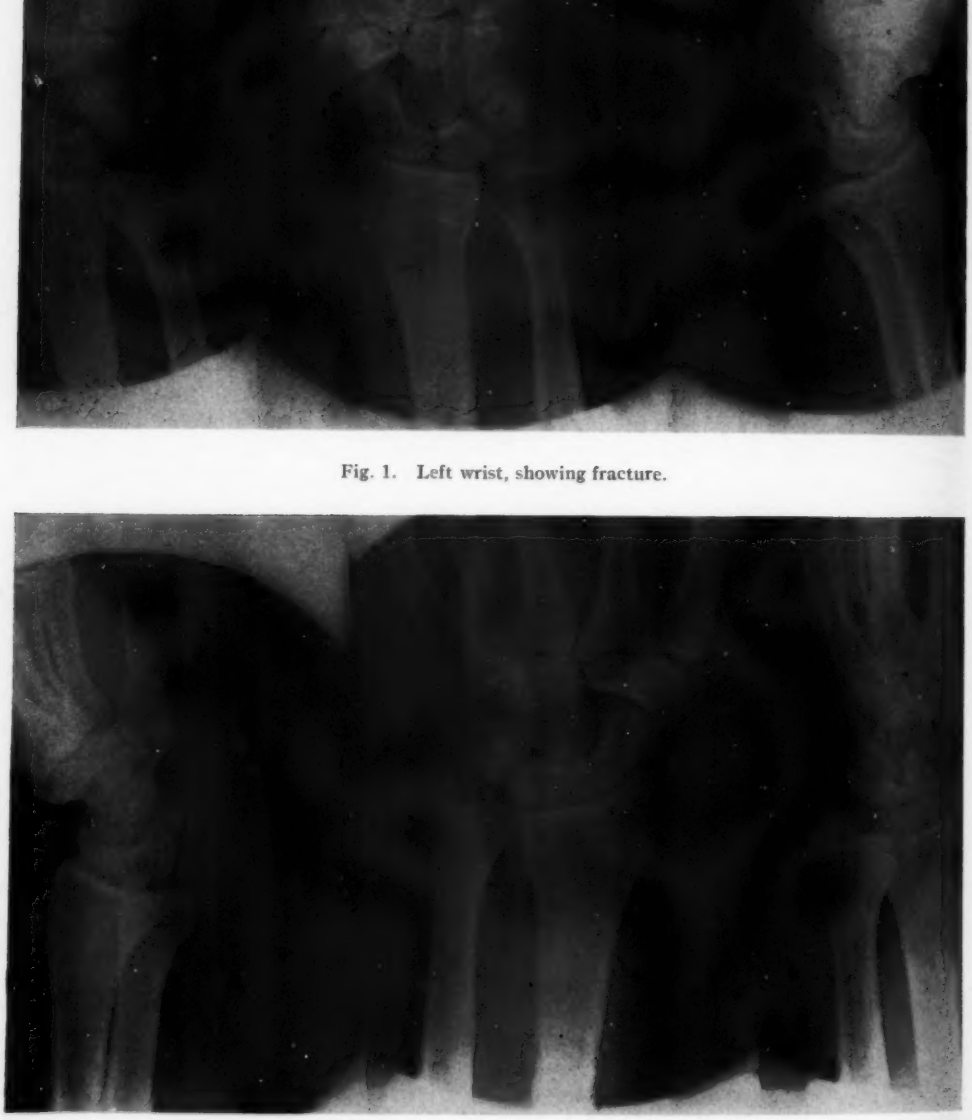

Fig. 2. Normal right wrist.

The recommended therapy is immobilization, and spontaneous healing usually occurs in about six weeks. If pain persists over three months, excision is advisable (19, 29). Healing generally seems to be by bony union, and in that event there is no

residual disability. Treatment is usually automatic when the fracture is a part of a more extensive injury, but it is of special importance to identify this fracture when it is solitary lest proper treatment be omitted.

The present case is that of a 22-year-old white male who was thrown from a motorcycle when he hit a rock in the road. He fractured his left clavicle, dislocated his right acromioclavicular joint, and injured his left wrist, the site of the pisiform fracture (Fig. 1). The mechanism of the injury was not clear. The right wrist (Fig. 2), studied for comparison, showed no abnormality. The patient had only slight pain in the wrist, which regressed after immobilization for one month.

In view of the fact that this injury may occur either as a solitary or concomitant fracture, it would seem wise to pay more attention to the pisiform bone in routine radiography of the injured wrist, and to include a lateral oblique view for its demonstration in cases of recent trauma accompanied by pain or tenderness over the ulnar aspect of the wrist.

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SUMARIO

Fractura Aislada del Hueso Pisiforme

La fractura del hueso pisiforme sin otras lesiones del carpo es extraña. Repásase la literatura y preséntase un caso. Para descubrir una fractura de ese género, puede necesitarse una vista oblicua en 80 grados de la muñeca, con el dorso virado hacia atrás, si bien en el caso descrito pudo verse fácilmente la lesión en la proyección palmar. El tratamiento es por inmovilización, y la cicatrización espontánea suele tener lugar en término de seis semanas, por unión ósea.

Regional Jejunitis

Three Cases[1]

COMDR. WILLIAM L. JANUS, (MC) USN

OF THE CASES OF regional enteritis reported since the description of that new disease entity in 1934, the greater percentage have involved the ileum. Until 1939 only 18 examples of regional enteritis of the upper small bowel had appeared in the literature (1, 2). To that number, 6 cases have subsequently been added.

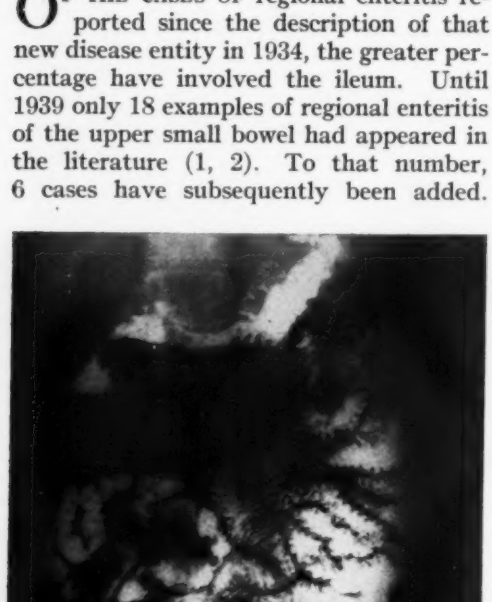

Fig. 1. Normal upper small bowel pattern after oral administration of barium mixture.

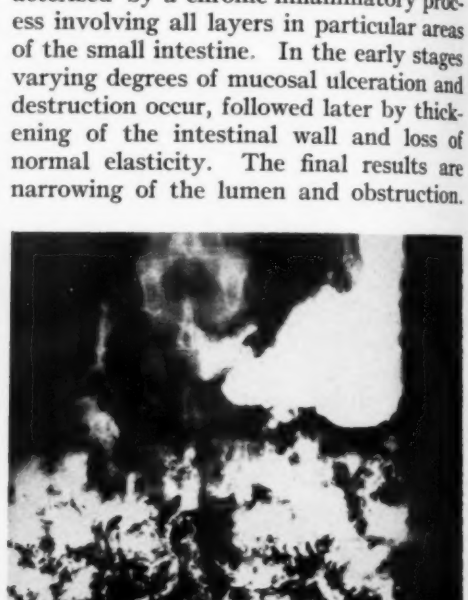

Fig. 2. Case I. Disturbed, fuzzy upper jejunal mucosal pattern, including spastic areas.

Regional jejunitis would thus appear to be a rare disease, but the question arises: Is it merely unrecognized?

Regional jejunitis is a serious illness. Six out of 9 patients in whom the condition was surgically proved were incapacitated or dead within two years, according to Pemberton and Brown (3).

Chronic regional enteritis is a definite pathological entity. Its etiology at the present time is undetermined. It is characterized by a chronic inflammatory process involving all layers in particular areas of the small intestine. In the early stages varying degrees of mucosal ulceration and destruction occur, followed later by thickening of the intestinal wall and loss of normal elasticity. The final results are narrowing of the lumen and obstruction. Numerous enlarged lymph nodes are always associated with the condition.

We present 3 cases of regional jejunitis, of which 2 were diagnosed preoperatively by roentgen examination. All were proved surgically and all were seen within a three-month period.

CASE I: J. L. S., male, aged 31, was admitted on March 12, 1946, complaining of loss of appetite, moderate nausea, abdominal pain, and loose stools. The symptoms were of several months' duration. The patient appeared in good physical condition, with tenderness to palpation in the right lower and

[1] Accepted for publication in June 1947.

middle abdominal areas. Laboratory findings were within normal limits. Roentgen examination of the upper gastro-intestinal tract revealed the diagnosis.

Roentgen Findings: Fluoroscopically, spasticity and irritability were observed along the distal greater curvature of the stomach, and near the duodenal-jejunal junction. Marked loss of normal mucosal pattern was noted throughout the duodenum and upper jejunum. This was due in part to increased motility of the barium meal through the involved areas, and in part to spasticity. There was associated tenderness on palpation. A tentative diagnosis of regional enteritis involving the proximal jejunum was made.

Operation on April 13, 1946, revealed jejunitis. The entire jejunum was thickened and rubbery, from duodenum to ileum. Associated mesenteric nodes were inflamed. There was no evidence of obstruction. A posterior gastro-low jejunostomy was performed. Eleven days later symptoms of obstruction developed, and an entero-enterostomy was done, bypassing the obstructed jejunal area.

The patient recovered after two months' stormy convalescence, but never returned to full duty. Postoperative upper gastro-intestinal roentgenographic studies showed a normally functioning gastro-ileostomy. No further follow-up studies are available.

CASE II: B. E. S., male, aged 22, was admitted March 13, 1946, complaining of loss of appetite and weight, nausea, loose stools for four weeks, and continuous cramping right abdominal pain. Laboratory examination was essentially negative. Physical examination revealed tenderness to palpation in the right lower abdominal area. No rigidity was present. On March 18, 1946, appendectomy was performed. Postoperative convalescence was complicated by gastric distention and retention. Nausea and vomiting followed.

Roentgen Findings: A small amount of barium mixture was given orally, after retained fluids were removed from the stomach. Fluoroscopically, marked irritability of the distal stomach and duodenum was present. Barium did not leave the third portion of the duodenum, and after progress films were studied, a diagnosis of distal duodenal obstruction was made.

Operative Findings: On March 26, 1946, the abdomen was again entered. The report was as follows: "Terminal duodenum and eighteen inches of the proximal jejunum showed thickened, beefy walls with many inflamed mesenteric lymph nodes. The duodenum at the point of exit from its retroperitoneal position was kinked to the right and bound to the jejunum by adhesions." A long-loop gastrojejunostomy was performed. The patient was well one month later, without complaints, but was medically discharged from the service because of the chronicity of the disease.

The findings in Case II are unusual, because the chronic inflammatory process involved a portion of the duodenum. Only a few cases of similar anatomical involvement are recorded in the literature (1, 3, 4).

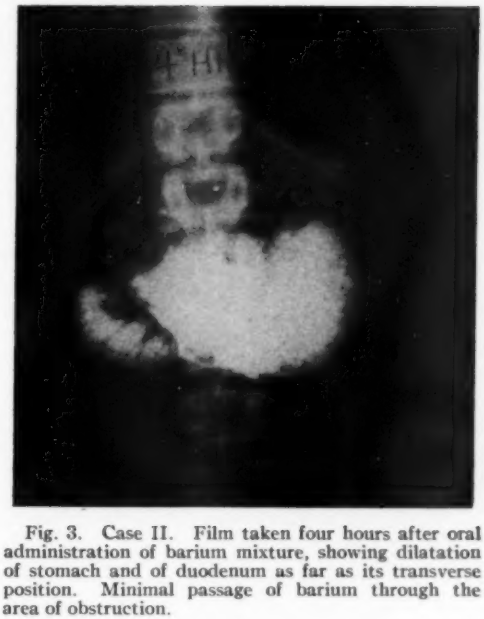

Fig. 3. Case II. Film taken four hours after oral administration of barium mixture, showing dilatation of stomach and of duodenum as far as its transverse position. Minimal passage of barium through the area of obstruction.

CASE III: C. L., male, aged 41, was admitted to the hospital May 8, 1946, complaining of nausea, vomiting, loose stools, and intermittent abdominal pain. All symptoms were of two years' duration and were increasing in severity. The final attacks of pain before admission were cramping in type, located in the mid-abdomen, and radiating to the left. As in the previous cases, laboratory studies were of no value in establishing a diagnosis. Physical examination was negative with the exception of tenderness in the left upper abdominal quadrant, radiating downward on pressure. No fever was noted, as was true also of the other two cases.

Roentgen Findings: Fluoroscopy after ingestion of a barium mixture outlined a normal stomach and duodenal cap. Marked increase in motility of the barium through the proximal jejunum was noted, accounting for the fuzzy, hazy appearance on progress films and the loss of feathery mucosal pattern. Tenderness was present over the involved loops, and spasticity causing segmentation could be induced. In the light of these findings, and on the basis of the progress films taken up to one hour, a diagnosis of regional enteritis involving the proximal jejunum was offered.

Operative Findings: On June 8, 1946, an exploratory examination was performed, revealing two and a half feet of the proximal jejunum involved by chronic inflammatory change, with enlarged mesen-

Fig. 4. Case III. Film made thirty minutes after oral administration of barium, showing segmentation, haziness, and loss of normal pattern throughout the proximal jejunum.

teric lymph nodes. The wall itself was thickened, with loss of normal mucosal luster. A gastrojejunostomy was performed, with the long loop anterior and contraperistaltic. Biopsy of a locally involved lymph node was reported as benign lymphadenitis, microscopically.

The postoperative course was uneventful and the patient was asymptomatic one month later. He was returned to duty on a limited diet.

In none of the cases reported here was resection of the small bowel performed. The problems and results of treatment are of surgical interest only and are not discussed in this paper.

DISCUSSION

Regional jejunitis and duodenitis may not be as rare as previously suspected. It seems possible that they may be overlooked roentgenologically, surgically and at autopsy. Routine gastro-intestinal studies often fail to demonstrate the condition. In the early stages, (1) irritability and (2) hypermotility of the barium meal through the involved portions of the bowel are characteristically present. This increased motility, I believe, gives the modified fuzzy, streaked appearance to the mucosal pattern as outlined by barium. In the presence of increased motility, suspected areas must be observed fluoroscopically and studied with "spot" films, in addition to routine progress films. Often careful re-examination of a previously "negative" gastro-intestinal tract will reveal chronic enteritis (4). Failure to make a diagnosis may be due to the fact that the clinician does not suspect the presence of the disease and does not insist upon careful small intestinal studies with contrast media. A chest film is essential to complete the diagnosis in all suspected cases of regional jejunitis, since it may be simulated by tuberculosis. Sprue and vitamin deficiency states must also be considered in the presence of a disturbed small bowel pattern (5).

This series of cases again proves that regional enteritis is not necessarily limited to the ileum, nor must it involve the ileum and proceed toward the stomach. This confirms the findings and deductions of Johnson (6). No definite etiological factor could be isolated in the present series. Certainly no previous history of bacillary dysentery was obtained, though this has been advanced as a possible etiological factor in the past. One patient (Case II) stated that his brother was afflicted by the same type of intestinal symptoms and had undergone several abdominal operations without relief.

SUMMARY AND CONCLUSION

1. Three surgically proved cases of regional jejunitis are presented, 2 of which also showed duodenal involvement.

2. Regional jejunitis is a serious condition with a high mortality and poor prognosis. It is evidently of more frequent occurrence than previous reports would indicate.

3. Radiographic findings vary from early inflammatory changes, as mucosa-abnormality and segmentation, to fibrol sis, thickening, and stenosis.

4. The greater curvature of the stomach may appear spastic and irritable at

fluoroscopy, due to the adjacent inflammatory process in the duodenum or jejunum.

5. The ileum is not necessarily involved in regional enteritis.

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SUMARIO

Yeyunitis Regional

Las enteritis regionales no tienen forzosamente que interesar el ileon. Aunque sólo ocasionalmente se ha comunicado invasión del yeyuno, puede que sea más frecuente que lo que indica la literatura.

Descríbense aquí tres casos de yeyunitis regional observados en un hospital en un período de tres meses, y en dos de los cuales también estaba afectado el duodeno. Los hallazgos roentgenológicos varían de alteraciones inflamatorias tempranas, en forma de anomalías y segmentación de las mucosas, a fibrosis, espesamiento y estenosis, más tarde. Roentgenoscópicamente, puede parecer que hay espasmodicidad e irritación de la curvatura mayor del estómago, debido al proceso inflamatorio adyacente en el duodeno o yeyuno.

Acute Gaseous Cholecystitis

Report of a Case[1]

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THIS INSTANCE OF gaseous cholecystitis is reported to illustrate the value of roentgenography in what appeared at first to be an uncomplicated choledocholithiasis.

The patient, a 60-year-old white butcher, entered the hospital in January 1947. He had been in excellent health until the age of 52, when a mild diabetes mellitus developed, which was controlled by diet. In mid 1945, an attack of mild aching in the right upper quadrant of the abdomen occurred, without nausea or jaundice. The attack lasted for one day. There was no history of an idiosyncrasy to fried or fatty foods.

On Jan. 18, 1947, about four hours after a roast pork dinner, the patient experienced a severe, steady, non-radiating pain in the right upper quadrant of the abdomen, with no nausea, vomiting, or chills. The pain subsided during the night, but a dull ache persisted. Two days later (Jan. 20), the patient was awakened at five o'clock in the morning by a recurrence of severe right upper quadrant pain, which continued with diminishing intensity throughout the day. He ate a light lunch and supper and that night vomited bile. He also noticed that his urine was dark and foul and that his stool was black. He was seen by a physician and given morphine for relief of pain. A dull ache continued, however, and on Jan. 22, four days after the initial attack, he was again awakened early in the morning by severe right upper quadrant pain. He was seen that morning by his physician, who noted the presence of jaundice. The patient felt somewhat better during the next three days but the jaundice and right upper quadrant ache persisted. He entered the hospital for study on Jan. 26, 1947.

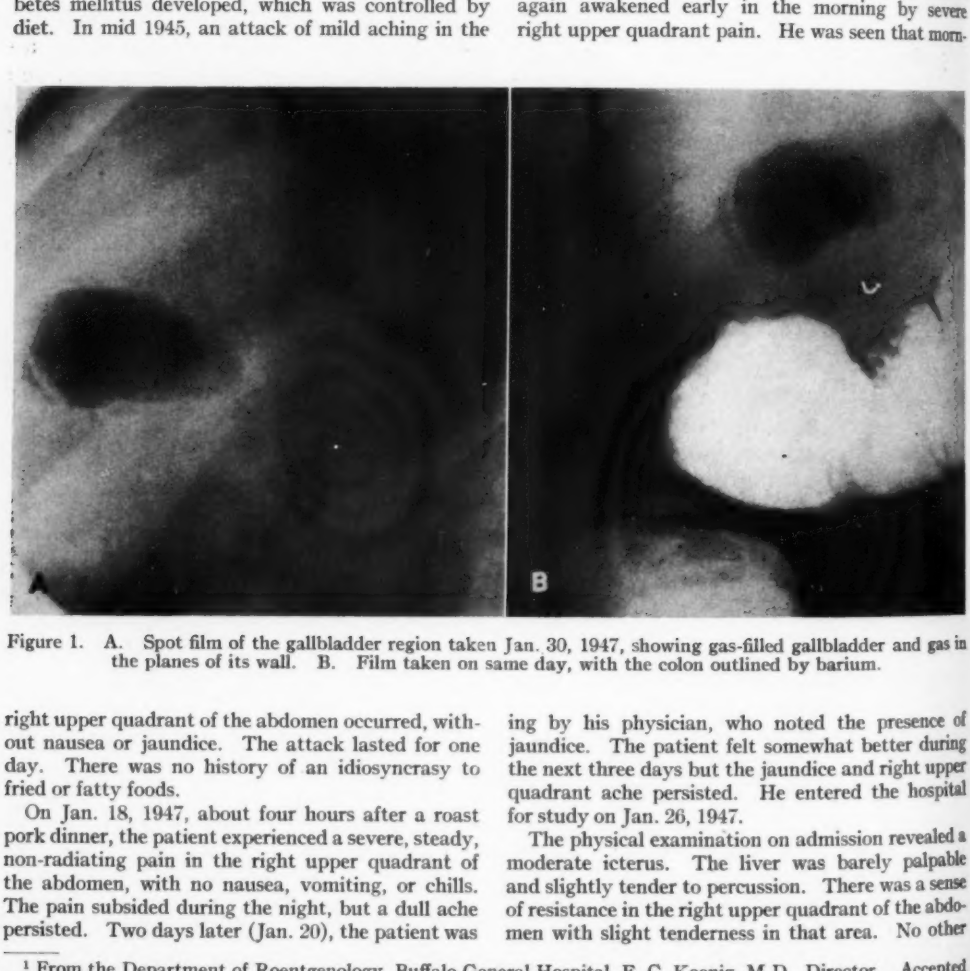

Figure 1. A. Spot film of the gallbladder region taken Jan. 30, 1947, showing gas-filled gallbladder and gas in the planes of its wall. B. Film taken on same day, with the colon outlined by barium.

The physical examination on admission revealed a moderate icterus. The liver was barely palpable and slightly tender to percussion. There was a sense of resistance in the right upper quadrant of the abdomen with slight tenderness in that area. No other

[1] From the Department of Roentgenology, Buffalo General Hospital, E. C. Koenig, M.D., Director. Accepted for publication in June 1947.

abnormalities were noted. The temperature ranged between 100 and 102° F.

Laboratory examinations revealed a slight elevation of globulin (3.9 gm. per cent) with normal albumin. The cephalin flocculation test was four plus. The thymol turbidity was within normal limits. The alkaline phosphatase was elevated, its highest level being 16.6 Bodansky units. The prothrombin time was slightly elevated. The van den Bergh reaction was prompt, with a reading of 14.8 mg. per cent. The white blood count and differential count were normal. The red blood count was 4,800,000 on admission but this figure subsequently dropped to 3,800,000.

Roentgen examination of the upper gastro-intestinal tract on Jan. 28, with contrast material, showed rather marked spasm of the prepyloric portion of the stomach, but no intrinsic lesion was demonstrated. During a review of the films on the following day, a persistent, rounded gas shadow was observed in the gallbladder area. On spot films this appeared to be a gas-filled gallbladder with gas penetrating the mucosa and lying in the planes of the gallbladder wall. A barium enema study was done to rule out the possibility that the shadow might represent gas in the colon. From the above studies, a diagnosis of gaseous cholecystitis was made.

The patient was given 100,000 units of penicillin every three hours, plus sulfadiazine in regular dosage. He gradually improved and was afebrile on the eighth day after initial treatment.

The gallbladder region was again studied with plain films on Feb. 1. There was no change in the appearance of the gas shadow. On Feb. 6, however, it was somewhat smaller. The diffusion of the gas into the gallbladder wall was still present, and, in addition, gas was now demonstrable within the cystic and common ducts. On Feb. 11 the gas shadow was still present, but was definitely smaller. No gas was seen in the extrahepatic passages at this time.

A duodenal drainage also was done on Feb. 11, but no gas-producing organisms were obtained on culture. There were copious amounts of "A" bile, and a smaller amount of "B" bile after magnesium sulfate. No pus cells or cholesterol crystals were present. No blood was present at any time in the duodenal contents or stools.

Clinically there was no icterus after Feb. 6, which was about one week after the institution of therapy, and the patient had no complaints during the latter part of his hospital stay. The alkaline phosphatase remained elevated, being 16.6 Bodansky units on the day of discharge, Feb. 19.

The patient was followed at home by his physician. Plain films of the gallbladder area obtained on Feb. 22 showed no gas in the gallbladder. Subsequently slight icterus developed and there was again some discomfort in the right upper quadrant of the abdomen. Another roentgen examination of the gallbladder area was done on March 17. Plain films showed gas in the gallbladder area, but it did not conform to the contour of the organ. It was believed to represent a recurrence of the anaerobic infection in the gallbladder area. Determination of alkaline phosphatase at that time showed 14 Bodansky units. The total cholesterol was 216 mg., and the cholesterol esters 37 mg. per cent. The albumin-globulin ratio was 3.6/4.0, the cephalin flocculation was four plus, and the urinary urobilinogen titer 1/40. The liver was now easily palpable, smooth, hard, and moderately tender. The spleen was not palpable. We believe the jaundice now to be intrahepatic, due to a pericholangiohepatitis. The diabetes is unchanged, and is controlled by insulin and diet.

Fig. 2. Film taken Feb. 6, 1947. In addition to gas within the gallbladder and in the gallbladder wall, gas shadows are seen in the extrahepatic ducts.

McCorkle and Fong, in 1942, thoroughly reviewed the literature on gaseous cholecystitis and reported three cases of their own. The first case was not recognized preoperatively and death from a fulminating anaerobic infection followed surgery. The other two cases were diagnosed roentgenographically and were treated conservatively, with complete recovery.

McCorkle and Fong outline the roentgenographic differential diagnosis between gas in the biliary system due to a communication with the intestinal tract, and that due to infection with a gas-forming organism. Uusually, when the gas arises by communication with the intestinal tract,

the cystic duct, hepatic ducts, and common bile duct are seen. The gallbladder itself is contracted, or is not seen at all. When the gallbladder can be seen, the gas is confined to the lumen. On an upright film, no fluid level can be demonstrated in the gallbladder. These authors advocate conservative treatment at all times. They believe that even interval cholecystectomy is contraindicated.

The first case of gaseous cholecystitis diagnosed roentgenographically was reported by von Friedrich in 1929. Up to 1942, 8 cases of gas infection of the gallbladder had been reported.

Hegner reported one case of gaseous cholecystitis which was demonstrable on the roentgen film and clinically on palpation. The patient was operated upon and made a good recovery until the fourth postoperative day, when he died from a massive pulmonary embolus. Schmidt also reported this case. It is interesting to note that the film demonstrated three of McCorkle and Fong's four criteria for the roentgen diagnosis of gaseous cholecystitis, namely, non-visualization of the duct system, a gallbladder of normal size, and gas in the gallbladder wall.

Our case of gaseous cholecystitis, diagnosed roentgenographically, is reported because of the comparative rarity of the preoperative diagnosis of such lesions and to show again the value of roentgen examination in the diagnosis of this condition.

NOTE: We wish to express our appreciation to Dr. Elmer Milch of the Department of Surgery and Dr. Alfred Lenzner of the Department of Medicine for their kind cooperation and valuable assistance in compiling and arranging clinical data.

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SUMARIO

Colecistitis Gaseosa Aguda

Comunícase un caso de colecistitis gaseosa para demostrar el valor de la roentgenografía en lo que parecía ser al principio coledocolitiasis simple. Una película gastrointestinal reveló una sombra redonda y persistente de gas en la zona de la vesícula biliar. Una película retocada reveló la vesícula biliar llena de gas y gas en los planos de la pared vesicular.

Accidental Filling of Urinary Tract During Barium Enema

Report of a Case[1]

S. PAUL PERRY, M.D., and W. DAN HADEN, M.D.

Sayre, Penna.

FISTULOUS communications between the intestinal tract and the urinary bladder are not rare, and the diagnosis is usually simply made. However, in a recent case seen in this clinic, this lesion was so dramatically demonstrated during the course of administration of a barium enema that the incident is considered unusual enough to form the basis of a case report.

The patient was a 65-year-old woman, who was referred to the X-Ray Department with a diagnosis of "diverticulitis and stricture in the sigmoid region." No other information was supplied.

At the beginning of the examination the rectal ampulla ballooned out well and there was then some delay at the rectosigmoid junction. At this time barium began to escape around the rectal nozzle but, as no signs of discomfort appeared, the examination was continued. In rotating the patient to examine the rectosigmoid region more thoroughly, a large, smoothly margined, barium-filled viscus was seen anteriorly and was thought to represent a redundant sigmoid. When the patient was returned to the supine position, a streak of contrast medium was observed moving from the pelvic region up toward the head. At first this was believed to be barium on the table top, since the enema was coming out as fast as it was going in. It soon became apparent that it really was barium flowing up the right ureter, since the right kidney pelvis became filled. The flow of barium from the can was immediately stopped, but by this time the left ureter was filled and the left renal pelvis partially so.

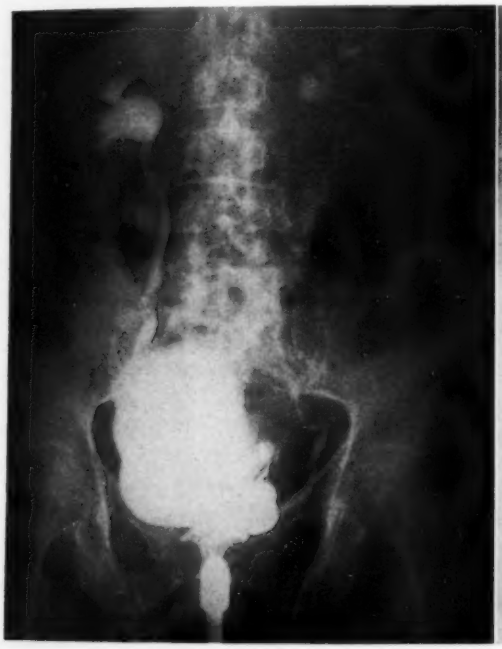

Fig. 1 (left). Anteroposterior view showing barium-filled bladder and rectum, right ureter, and kidney pelvis partially filled left ureter and kidney pelvis.
Fig. 2 (right). Lateral view showing rounded mass of the distended urinary bladder.

[1] Accepted for publication in May 1947.

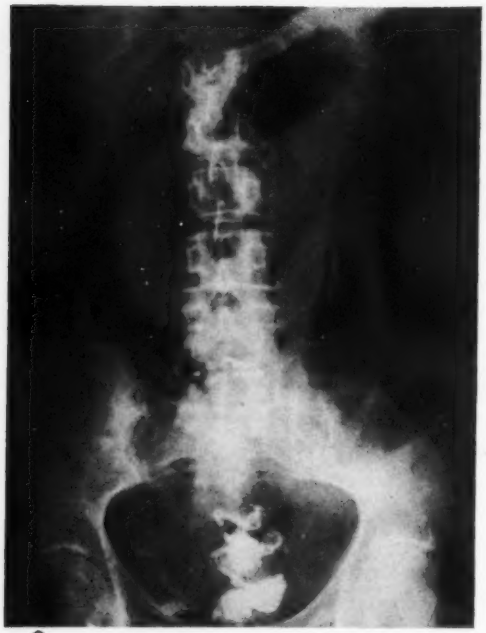

Fig. 3. Follow-up film obtained approximately five hours after those in Figs. 1 and 2, showing slight residual barium in the lower end of the right ureter.

Films were made quickly, and the enema can was lowered to the floor to allow as much of the contrast medium as possible to run out. The rectum and what apparently was the urinary bladder were almost completely emptied before the patient left the examining table. Another film was made approximately four hours after the original examination. The kidney pelves were clear, as were both ureters except for a small residuum of barium in the terminal portion of the one on the right.

In checking the patient's clinical chart, it was found that some years previously she had had a perforated sigmoid diverticulum, following which there had been all the signs of a rectovaginal fistula—passage of gas and feces by the vagina, etc. More recently she had been passing some feces and gas when urinating. A proctoscopic examination had been attempted but, because of scar tissue in the rectosigmoid, was not satisfactory.

There were no ill effects from the experience and the patient's kidney function did not seem to be impaired in the least, as was shown by a normal intravenous pyelogram the following day. A colostomy was later performed, preparatory to a repair of the fistula, and the patient was doing well at the last report.

The unusualness of this situation, which, as far as we could determine, is rarely encountered, prompted us to prepare and submit this case report. In the presence of good kidney function and no gross abnormalities of the urinary tract which would lead to delayed return of the contrast medium, it would seem to us that the danger of complication is negligible.

Guthrie Clinic
Robert Packer Hospital
Sayre, Penna.

SUMARIO

Henchimiento Accidental del Aparato Urinario Durante un Estudio con un Enema de Bario

En el transcurso de un estudio con un enema de bario en una mujer de 65 años, se observó un relleno inesperado de las pelvis renales y los uréteres. Al suspender la administración, la sustancia de contraste fué devuelta rápidamente, sin observarse malos efectos. Más tarde, se obtuvo una historia de fístula rectovaginal consecutiva a perforación de un divertículo sigmoideo algunos años antes.

EDITORIAL

Cancer Detection Clinics

Well-patient clinics or examination centers, commonly called "Cancer Prevention," "Cancer Detection," or "Health Maintenance Clinics," have captured the imagination of the public and today great pressure is being exerted upon the medical profession to inaugurate such clinics in many communities. It is interesting to remind ourselves that for years county medical societies and their parent body, The American Medical Association, have sponsored and stimulated yearly physical examinations. In spite of all kinds of propaganda, yearly examinations did not excite very much interest among physicians or the public. This lack of interest in yearly physical examinations, both on the part of physicians and the public, was to be expected for several reasons: medical schools even today do not, as a rule, emphasize the importance of general physical examinations in well people; the medical student is more interested in disease; the apparently healthy public is not educated to the necessity or value of yearly examinations, and doctors generally neglect their own health.

The value of periodic medical examinations has received great emphasis from the educational program of the American Cancer Society, the experience obtained in the "Selective Service System," and the pilot experiments of Dr. Elise S. L'Esperance in New York City, of Dr. Catherine Macfarlane, Dr. Margaret C. J. Sturgis and Dr. Faith S. Fetterman in Philadelphia, the Cancer Prevention Clinics of the Donner Foundation, and those of Dr. Augusta Webster and her colleagues in Chicago.

The well-patient clinic or the detection center is not a diagnostic center; it is not a tumor clinic. It is not designed for cancer patients, but it is an examination center, organized for the examination of apparently well people. Its primary objective is to detect early cancer, precancerous lesions, or areas of chronic irritation which might lead to cancer, sooner than they would otherwise be discovered. The examination includes all of the studies that can be obtained from any good general practitioner. The centers do not give treatment nor do they undertake such procedures as biopsy. Their function is to provide a thorough physical examination with special emphasis on conditions which might lead to cancer. Early manifestations of other diseases also are detected.

The name "Cancer Prevention Clinic" has been adopted by many groups. Others prefer "Cancer Detection Clinics." "Examination Centers" or "Health Maintenance Clinics," although perhaps more correct, do not attract the public's attention to the same extent.

Dr. J. R. Miller (1) of Hartford, Conn., has stated:

"I am not at all sure that the detection clinic has come to stay. Certainly if general practitioners undertake this work satisfactorily in their own offices, there should be no place for it. Perhaps its chief service is going to be in teaching the technic of a rapid screening type of examination. Time alone will tell. For the present we must face the fact that the public is highly interested, as never before, in the annual physical examination and has been sold on the idea of going to a clinic. I believe the American Cancer Society, though responsible to a large extent for creating this interest in being examined, is not entirely responsible for the clinic idea. Those of us who live in the smaller metropolitan centers have for many years seen our patients attracted to organized clinics of the large cities. The profession must approve of these clinics, for general practitioners send many patients to them, and clinic physicians are among our best medical teachers, listened to attentively by thousands of physicians. The heads

of these clinics have been singularly honored, also, by organized medicine.

"I believe there is developing an opportunity for physicians organized in their local communities to give the public all of these advantages by co-operating with the philanthropic institutions and with the public health services. They can control this situation in which they must of necessity play the leading role."

Dr. R. R. Newell (2) of San Francisco, Calif., has pointed out the following practical points concerning cancer detection clinics:

"Every doctor is well aware of the fact that very few physicians submit themselves to regular 'birthday examinations.' Doctors are notoriously careless of their own health, but even so the above is some measure of doctors' general estimate of the value of a routine examination of a person who does not believe himself ill.

"In 6,000 pelvic examinations on apparently well women, Footer found 3 early cases of cervical cancer. Eight hundred symptomless persons over 45 had to be fluoroscoped in order to find one gastric cancer. The discovery cost in doctors' time per cervix case is roughly 400 hours plus overhead (at 5 per hour); per gastric case, 160 hours. Early cancer is not to be detected by a person without some experience. I mean, these have to be done by expensive talent. The discovery cost in money in these fields might be, then, $7,000 or $8,000; not too high a price to pay for getting a good chance to escape a desperate disease!

"But the economics is very different from what it is in tuberculosis case finding by photofluorography, where the discovery cost runs about 1 per cent as much and where every case discovered and controlled lessens the tuberculosis hazard to everybody else in the city.

"To examine every middle-aged woman every year (for uterine cancer) would take eight hours a day by 1,000 doctors.

"To fluoroscope the stomachs of middle-aged men, say 500 doctors.

"We could do this job by mobilizing 1 per cent of our medical talent.

"As we train more doctors—if we do—so that doctors in general are not too busy to take adequate care of the people who know they are ill; and as we solve other medical problems, leaving cancer to become more and more important statistically, we may find cancer detection the next thing to take up. But at present it is just not in the same class with tuberculosis case finding (by two orders of magnitude) and it needs to be demonstrated that to drain off the required portion of better trained medical talent for cancer detection might not be more than the rest of medicine can today afford.

"Although the second most frequent cause of death, yet cancer is still but a small part of human illness. A busy doctor will see two or three new cases of cancer a year. The rest of his time goes to caring for other illnesses. It is not yet obvious that he will be wise to spend one per cent of his time trying to better (by early detection) the results in one per mille of his work. There is an unnamed legion of other medical problems that could well use one per cent of doctors' time, too; not to mention the good that would come if doctors gave an extra 1 per cent of their time to graduate medical education (many already give a week per year, which is 2 per cent).

"It is true that a human life is priceless, and that discovery of a case of cancer in a curable stage is worth any amount of money and effort. But this philosophy can be applied to only one person. If you apply it to everybody, you run into the difficulty that time and money are available in only finite amounts and must be allocated to all the other essential things of living.

"At present, Cancer Detection Clinics must be looked on as pilot plants to explore: (*a*) the statistical success attainable in detection, and (*b*) the amount of medical talent available to be deviated to this effort."

Radiologists are participating in the program of the cancer detection clinic, and the cancer detection clinic as a pilot experiment has been endorsed by the College of Radiology. The Committee on Public Health of the College believe, however, that only a "tiny fraction of the whole population" can be reached by the so-called cancer prevention clinic and that the success or failure of any cancer control program is going to depend in large measure on the skill, knowledge, and attitude of the attending physician or family doctor. The program must assist and not compete with practitioners of medicine.

EUGENE P. PENDERGRASS, M.D.

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Membership Elect

We have been impressed with the fairly large number of young radiologists who have attended recent annual conventions of the Radiological Society of North America as guests rather than as members. The fact that many of these enthusiasts are not members is further borne out by a study of the Reports of the Secretary in the Annual Members' Handbook. This shows that year after year the new members practically all join as active members rather than as members-elect.

Today, most residents in training to become radiologists doubtless feel that their daily academic pursuits permit them little or no time for consideration of the organizational aspects of radiology. Their indoctrination in many instances has been such that they probably believe they cannot qualify until they have become certified by the American Board of Radiology. This, however, is not the case.

To beome a *member-elect* one must have the following requisites:

1. M.D. degree or equivalent.
2. Citizenship in the North American country of residence.
3. Membership in the A. M. A. or equivalent group.
4. The major part of the year immediately preceding the application must have been devoted to work in radiology.
5. Payment of dues ($15.00).

After two years a member-elect is eligible to apply for active membership in the Society.

We believe that trainees in radiology would welcome the opportunity of joining the leading radiological society and in sharing some of the obligations as well as the privileges of radiology. We know of no better way of starting such a program than by application for membership-elect.

It is therefore suggested that staff and consulting radiologists in hospitals approved for resident training and State Counselors of the Radiological Society of North America initiate steps in this direction. At the same time, it must be stated that we believe certification is an ultimate desideratum for every member-elect as well as for all active members.

L. HENRY GARLAND, M.D.

ANNUAL MEETING, 1948 RADIOLOGICAL SOCIETY OF NORTH AMERICA

San Francisco has been chosen by the Directors of the Radiological Society of North America for the Thirty-fourth Annual Meeting, Dec. 5–10, 1948, headquarters to be the Fairmont and Mark Hopkins Hotels.

It is suggested that you make your hotel and transportation arrangements at the earliest possible date. Railroad, airplane and ship accommodations are ample.

Members wishing to present papers or scientific exhibits are asked to write as soon as possible to the Program Committee, Room 1739, 450 Sutter St., San Francisco 8, giving the title and a fifty-word abstract of the intended presentation.

Act Now—It is Later Than You Think

AMERICAN RADIUM SOCIETY

The following preliminary program has been announced for the meeting of the American Radium Society at the Stevens Hotel, Chicago, June 20–22, 1948.

Sunday, June 20: 8:00 A.M.–12:00

Refresher Courses
- Experimental Comparison of Gamma and Roentgen Rays in Serial Biopsies, Constance Wood
- Intra-oral Cancer, Elis Berven
- Cancer of Pharynx and Larynx, Francois Baclesse
- Cancer of Uterus, Juliette Baud
- Cancer of Penis, Sir Stanford Cade and B. W. Windeyer

Monday, June 21

8:00–9:00: Refresher Course
- Carcinoma of the Antrum, Sir Stanford Cade and B. W. Windeyer

9:00–9:20: Presidential Address

9:20–9:30: Statistics, Eleanor J. MacDonald

9:30–12:30

Panel Discussion: End-Results of Treatment of Cancer of the Tongue
- *Moderator:* Douglas Quick
- *Discussants:* Juliette Baud, Elis Berven, Sir Stanford Cade, H. E. Martin, G. E. Richards, B. W. Windeyer, Constance Wood

1:30–2:00: Executive Session

2:00–4:00

Panel Discussion: Should Radiotherapy be Separated from X-Ray Diagnosis
- *Moderator:* Aubrey O. Hampton
- *Discussants:* Elis Berven, Ross Golden, B. R. Kirklin, Robert R. Newell, B. W. Windeyer

4:30: Janeway Lecture
The Achievement of Radium in the Fight Against Cancer, Sir Stanford Cade

7:00: Banquet
Oration: Fifty Years of Radium, Edith H. Quimby

Tuesday, June 22

8:30–9:30: Refresher Course, Robert McWhirter

9:30–12:30

Panel Discussion: Treatment and Results in Cancer of the Breast
- *Moderator:* Maurice Lenz
- *Discussants:* Francois Baclesse, Elis Berven, Sir Stanford Cade, Cushman D. Haagensen, Grantley W. Taylor, R. McWhirter, B. W. Windeyer

1:30–2:00: Executive Session

2:00–4:00

Roentgen Therapy of Advanced Cancer of the Cervix, Francois Baclesse

Contact X-ray Therapy of Cancer of the Rectum, Paul Lamarque

Treatment of Metastatic Cancer of the Breast, J. R. Freid, H. Goldberg and A. Herrman

Cancer of the Ear, C. L. Martin and J. A. Martin

Radium Therapy of Advanced Salivary Gland Tumors of the Palate, Max Cutler

Radium Therapy of Bartholin Gland Cancer, H. H. Bowing, R. E. Fricke and T. J. Kennedy

LONG ISLAND RADIOLOGICAL SOCIETY

At a recent meeting of the Long Island Radiological Society, the following officers were elected for the ensuing year: President, Dr. Max Dannenberg; Vice-President, Dr. Henry G. Koiransky; Secretary, Dr. Marcus Wiener; Treasurer, Dr. I. Spencer Silverstein.

The Society meets every fourth Thursday evening at 8:45 P.M., October to May.

RADIOLOGICAL SECTION DISTRICT OF COLUMBIA MEDICAL SOCIETY

There has recently been added to the list of regional radiological societies a Radiological Section of the District of Columbia Medical Society. The meeting place is the Medical Society Auditorium; the dates, the third Thursday of January, March, May, and October, at 8:00 P.M. The Secretary of the new organization is Dr. Alfred A. J. Den, 1801 K St., N. W., Washington 6.

Letter to the Editor

FEE SPLITTING AND REBATES

To the Editor:

Dear Dr. Doub:

I am writing you at the suggestion of Dr. Wilbur Bailey concerning the concerted program of the Los Angeles Radiological Society in connection with a local problem of fee splitting and rebates. This has been going on a number of years in our community, to the detriment of the public and of good medical practice. The Society was approached some time ago by the Better Business Bureau of Los Angeles requesting cooperation in clearing up the situation since they had received no real cooperation from the Los Angeles County Medical Association, asking that the doctors clean their own house. We agreed to cooperate with the Better Business Bureau if they would sponsor the program, we to act only as advisers. As you have undoubtedly heard on the radio and seen in the newspapers, a concerted drive has been made by the Better Business Bureau and I believe the campaign is already bearing fruit.

For the first time in its history, the Council of the Los Angeles County Medical Association in special session on Jan. 15, 1948, took definite action on the problem of rebates. They have issued notice to all members that the Council will institute disciplinary action against any member charged with rebating and that expulsion from the Los Angeles County Medical Association will be the penalty if such a member is convicted. Following is the resolution that the Council issued to all of its members:

"*Be it resolved* that any physician who accepts a rebate is guilty of unethical conduct and that such conduct is incompatible with membership in the Los Angeles County Medical Association.

"As the term 'rebate' is used herein, it means money, credits, or anything of value, which is received, directly or indirectly, in any guise whatever, by the referring physician from any person, partnership, or corporation, profit, non-profit, or cooperative, to whom a patient or any person is referred or sent for medical or laboratory services, or for medical or professional device, equipment, materials, or supplies."

The campaign has spread throughout all of California and definite action has already been noted in the Los Angeles area, as well as in the San Diego area. In San Diego the City Council has passed legislation making rebating or fee splitting a misdemeanor and we are under assurances from the California Medical Association that a measure will be introduced in the state legislature for legislation concerning the matter.

All of us feel, although circumstances required airing of the problem in an unfortunate manner, it will result in better practice of medicine and in better relations between practitioners of medicine.

Sincerely yours,

MORIS HORWITZ, M.D.
Secretary, Los Angeles Radiological Society

In Memoriam

ALBAN KÖHLER

1874–1947

Already in these columns there has appeared brief notice of the death of Dr. Alban Köhler, of Wiesbaden, on Feb. 26, 1947. It is fitting, however, that a more detailed reference be made to the passing of this great man.

Dr. Alban Köhler

Alban Köhler was born in Petsa in Thüringen, March 1, 1874. He broke away from his farmer ancestry and environment to acquire a classical education, and finally studied medicine in Freiburg, Erlangen, and in Berlin, graduating in 1899. After three years of surgery at St. Joseph's Hospital in Wiesbaden, he established himself as a radiologist in 1902. He had already written a book on roentgenography of diseases of the bones (1901); in 1905 he published a book on the hip joint and the femur, and in 1906 one on the x-ray diagnosis of pulmonary tuberculosis in children. His most important work, however, and one which made him famous the world over, was his book, "The Borderlands of the Normal and the Early Pathological as Seen with the X-ray." The first edition of this work was published in 1910 and it has been reissued with annotations and enlargements through eight editions, with the ninth edition in preparation at the time of the author's death. This book has appeared in all the principal world

languages, including English, and its importance is such that it has come to be known as the "radiologist's Bible."

Dr. Köhler's name stands high on the list of pioneers in radiological science; his life is a long record of investigation and exemplary practice as a clinical radiological specialist and he is regarded the world over with gratitude and respect. His life, in many ways, resembles the career of our American Dr. A. W. Crane. He did not choose to set up his work in a university city, though he received many offers of positions of executive and scientific importance in hospitals and universities. He chose to live his life as a private practitioner, but he was so enthusiastic and capable in his clinical research that he was able to contribute in an important way to the advancement of radiology not only by his outstanding book on the borderlines of the normal and the beginnings of the pathological, but also through numerous contributions to radiological and other medical society meetings.

Dr. Köhler was one of the first to outline a practice of radiology of the heart, describing the relation of the teleroentgenogram to the orthodiagram; other contributions covered a method of localization of foreign bodies in the eye; stereoscopic films and cinematographic study of the respiratory tract; calcific placques in the aortic arch, and an osteochondritic disturbance of the foot, which is known as Köhler's disease.

In spite of the fact that he began his work early in the roentgen era, when there was little knowledge of the harmful effects of the rays, Dr. Köhler was fortunate to escape severe x-ray damage.

At the time of his death he was busily engaged in the preparation of his memoirs and in editing the manuscript for the ninth edition of his important work on "Borderlands." It is to be hoped that the Memoirs may someday be published. The ninth edition of his "Borderlands" work was already partly printed when a bombing raid destroyed the publishing house. His home in Wiesbaden, in which he had his office and radiological institute and a very important radiological library, was also destroyed by fire following a severe air attack. He had already lost his wife and only son.

During the last year or two of his life, particularly through a notice published in the pages of RADIOLOGY, Dr. Köhler derived much satisfaction from renewing contacts with many of his friends in the United States.

JAMES T. CASE, M.D.

HARRY LAWRENCE FARMER

1895–1947

Dr. Harry L. Farmer died suddenly at his home in Shaker Heights, Cleveland, Ohio, on Dec. 6, 1947, of coronary thrombosis, at the age of fifty-two. He had just returned from the annual meeting of the Radiological Society of North America in Boston, where he had enjoyed meeting his fellow radiologists and had attended the scientific sessions and refresher courses regularly. His reunion with many old friends at the dinner for Doctor George Holmes was a particular pleasure.

Dr. Farmer was a veteran of World War I, having served in the Medical Corps, U.S.N.R., in 1918 and 1919, following his graduation from Baylor University Medical School. He served his internship at Cincinnati General Hospital and received his training in radiology under Dr. George Holmes at Massachusetts General Hospital during the years 1921–1923. In 1923 Dr. Farmer went to Cleveland as chief of the x-ray service at City Hospital, and shortly thereafter he was elected to membership in the Radiological Society of North America. He was a charter member of the Cleveland Radiological Society, founded in 1923. He soon entered into partnership with Dr. Walter Hill, Dr. George Thomas, and Dr. Merthyn Thomas, with whom he continued to practise. He was elected to membership in the American Roentgen Ray Society in 1928 and became a diplomate of the American Board of Radiology in 1934, and a Fellow of the American College of Radiology in 1937.

During his active professional and civic life in Cleveland, Dr. Farmer was a member of the Board of Directors of the Cleveland Academy of Medicine from 1937 to 1939. He was active in the affairs of the Euclid Avenue Christian Church, of which he was a member for many years. The charm of his personality was based on his real liking for people; no task was too great for him to undertake for a friend. In his professional work he exhibited a meticulous intellectual honesty which made association with him a rewarding experience.

Dr. Farmer is survived by his wife, Mrs. Mary Snider Farmer, and three sons: William, who graduated from Case Institute of Technology in 1947; James, a sophomore at Dartmouth College, and Harry, Jr., a sophomore at Shaker Heights High School.

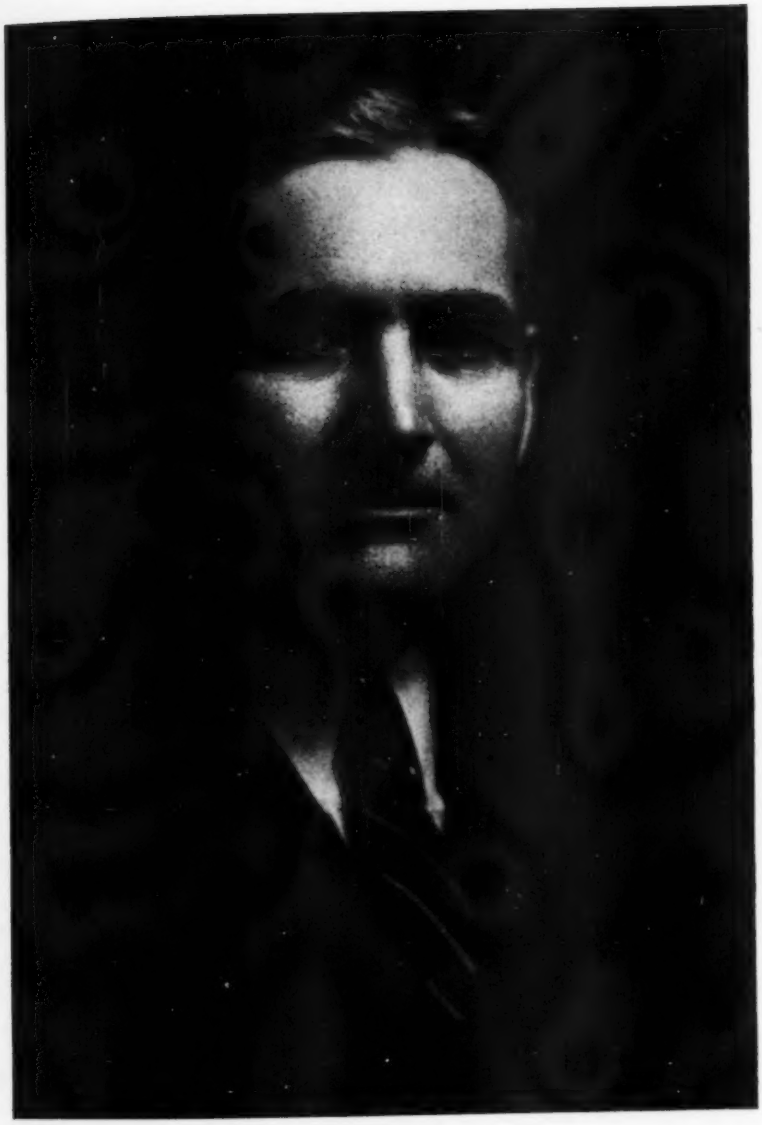
Dr. Farmer's birthplace and family home was Comanche, Texas, and his body was returned there for burial.

GEORGE L. SACKETT, M.D.

Book Reviews

ELECTRONICS AND THEIR APPLICATION IN INDUSTRY AND RESEARCH. Edited by BERNARD LOVELL, O.E.B., B.Sc., PH.D., F. INST. P., Physical Laboratories, University of Manchester. A volume of 660 pages, with 404 illustrations. Published by the Pilot Press, Ltd., London, 1947. Price 42s net.

Each of the sixteen chapters of *Electronics and Their Application in Industry and Research*, relates to a specific subject and each is written by an outstanding expert in that particular field. The first



HARRY L. FARMER, M.D.
1895–1947

chapter, by the editor, Bernard Lovell, goes into considerable detail as to the history of electronics, with particular attention to the development of this subject within essentially the last twenty years. The first chapter to take up a specific subject, "Electron Physics" is written by F. A. Vick of the Physical Laboratories, University of Manchester. These particular laboratories are well known to radiologists for the excellent work done over many years on such subjects as radium and x-ray measurements. The chapter in itself is reasonably adequate but at times it is difficult to understand what type of audience the author is attempting to reach. The mathematical development will be beyond the range of most physicians, yet is not adequate for students of physics. The author has succeeded in condensing the fundamentals of many different fields of study on the nature and behavior of electronics and electrical currents into thirty-seven pages. Obviously, no field can be covered in detail.

Authors of subsequent chapters, having less comprehensive fields to cover, go into more detail and in general develop and analyze their subjects well. Most of them assume a rather complete fundamental knowledge on the part of the reader and go on from there to develop their particular thesis, with the results that any reader will find some chapters suitable to his use and others of much less interest.

For physicians in general and radiologists in particular, the last four chapters will be of most importance. Of this group, the first one, Chapter 9, entitled "Electronics in Medicine," is written by L. G. Grimmett, who has long been associated with certain phases of radiology. He proceeds, after a general introduction, to discuss high frequency, electron optics, electronics in registration of bio-electric potentials, electronic acoustics and photo-electric cells, all in connection with and as applied to medicine. He touches very lightly on the newer machines for the development of high-energy radiations for therapeutic use, and skims through an imposing array of other subjects. He does, however, do an excellent job of reducing these subjects to their minimum fundamentals and follows this by a bibliography of sixty-five references which are well chosen to give the reader further and more detailed information on any specific subject in which he is interested. Chapter 12, entitled "Electronics in Physiology" is very short and unfortunately spends a bit more than the necessary time in its seventeen pages on historical facts which form the basis for more modern studies. Chapter 13, entitled "The Betatron" goes into the study of this particular instrument in some detail and again leaves the reader somewhat confused by being too mathematical for the biological sciences and too descriptive for physical application. Chapter 14, "Electron Microscopy and Electron Diffraction," is actually a textbook in itself. In the course of its one hundred three well organized and well written pages, it develops the basic theory of the electron microscope, illustrates the degree to which this instrument has been developed at the present time, and gives an excellent survey of its applications and a considerable amount of information on the technics involved. The chapter is followed by a list of 106 references which include all of the important ones of construction technic and application, and a bibliography of seven additional books with a brief note on the particular application and value of each.

In general, this volume is a handy reference guide which will find a considerable application in any large department of radiology or research division of a hospital. Its main value lies in the fact that it gives a brief description and a ready reference to almost any subject in the general field of electronics. For example, a radiologist will be able to find quickly something on the nature of photo-cells or high-frequency induction heat without having to search in unfamiliar literature which may not be readily available. The book, therefore, makes a valuable laboratory handbook.

RADIOLOGICAL SOCIETIES: SECRETARIES AND MEETING DATES

Editor's Note: Secretaries of state and local radiological societies are requested to co-operate in keeping this section up-to-date by notifying the editor promptly of changes in officers and meeting dates.

UNITED STATES

RADIOLOGICAL SOCIETY OF NORTH AMERICA. *Secretary-Treasurer*, Donald S. Childs, M.D., 607 Medical Arts Bldg., Syracuse 2, N. Y.

AMERICAN RADIUM SOCIETY. *Secretary*, Hugh F. Hare, M.D., 605 Commonwealth Ave., Boston 15, Mass.

AMERICAN ROENTGEN RAY SOCIETY. *Secretary*, Harold Dabney Kerr, M.D., Iowa City, Iowa.

AMERICAN COLLEGE OF RADIOLOGY. *Secretary*, Mac F. Cahal, 20 N. Wacker Dr., Chicago 6, Ill.

SECTION ON RADIOLOGY, A. M. A. *Secretary*, U. V. Portmann, M.D., Cleveland Clinic, Cleveland 6, Ohio.

Alabama

ALABAMA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Courtney S. Stickley, M.D., Bell Bldg., Montgomery. Next meeting with State Medical Association.

Arkansas

ARKANSAS RADIOLOGICAL SOCIETY. *Secretary*, Fred Hames, M.D., Pine Bluff. Meets every three months and at meeting of State Medical Society.

California

CALIFORNIA MEDICAL ASSOCIATION, SECTION ON RADIOLOGY. *Secretary*, Sydney F. Thomas, M.D., Palo Alto Clinic, Palo Alto.

LOS ANGELES RADIOLOGICAL SOCIETY. *Secretary*, Moris Horwitz, M.D., 2009 Wilshire Blvd., Los Angeles 5. Meets second Wednesday of each month at County Society Bldg.

PACIFIC ROENTGEN SOCIETY. *Secretary*, L. Henry Garland, M.D., 450 Sutter St., San Francisco 8. Meets annually with State Medical Association.

SAN DIEGO ROENTGEN SOCIETY. *Secretary*, R. F. Niehaus, M.D., 1831 Fourth Ave., San Diego. Meets first Wednesday of each month.

X-RAY STUDY CLUB OF SAN FRANCISCO. *Secretary*, Ivan J. Miller, M.D., 2000 Van Ness Ave. Meets monthly on the third Thursday at 7:45 P.M., January to June at Lane Hall, Stanford University Hospital, and July to December at Toland Hall, University of California Hospital.

Colorado

DENVER RADIOLOGICAL CLUB. *Secretary*, Mark S. Donovan, M.D., 306 Majestic Bldg., Denver 2. Meets third Friday of each month, at the Colorado School of Medicine and Hospitals.

Connecticut

CONNECTICUT STATE MEDICAL SOCIETY, SECTION ON RADIOLOGY. *Secretary*, Robert M. Lowman, M.D., Grace-New Haven Hospital, Grace Unit, New Haven. Meetings bimonthly, second Thursday.

District of Columbia

RADIOLOGICAL SECTION, DISTRICT OF COLUMBIA MEDICAL SOCIETY. *Secretary*, Alfred A. J. Den, M.D., 1801 K St., N. W., Washington 6. Meets third Thursday of January, March, May, and October, at 8:00 P.M., in Medical Society Auditorium.

Florida

FLORIDA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, J. A. Beals, M.D., St. Luke's Hospital, Jacksonville. Meets in April, preceding annual meeting of Florida Medical Society, and in November.

Georgia

GEORGIA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Robert Drane, M.D., De Renne Apartments, Savannah. Meets in November and at the annual meeting of State Medical Association.

Illinois

CHICAGO ROENTGEN SOCIETY. *Secretary*, T. J. Wachowski, M.D., 310 Ellis Ave., Wheaton. Meets at the Palmer House, second Thursday of October, November, January, February, March, and April, at 8:00 P.M.

ILLINOIS RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, William DeHollander, M.D., St. Johns' Hospital, Springfield. Meetings quarterly as announced.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON RADIOLOGY. *Secretary*, John H. Gilmore, M.D., 720 N. Michigan Ave., Chicago 11.

Indiana

INDIANA ROENTGEN SOCIETY. *Secretary-Treasurer*, J. A. Campbell, M.D., Indiana University Hospitals, Indianapolis 7. Annual meeting in May.

Iowa

IOWA X-RAY CLUB. *Secretary*, Arthur W. Erskine, M.D., 326 Higley Building, Cedar Rapids. Meets during annual session of State Medical Society.

Kentucky

KENTUCKY RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Sydney E. Johnson, M.D., 101 W. Chestnut St., Louisville.

LOUISVILLE RADIOLOGICAL SOCIETY, *Secretary-Treasurer*, Everett L. Pirkey, Louisville General Hospital, Louisville 2. Meets second Friday of each month at Louisville General Hospital.

Louisiana

LOUISIANA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Johnson R. Anderson, M.D., No. Louisiana Sanitarium, Shreveport. Meets with State Medical Society.

ORLEANS PARISH RADIOLOGICAL SOCIETY. *Secretary*, Joseph V. Schlosser, M.D., Charity Hospital of Louisiana, New Orleans 13. Meets first Tuesday of each month.

SHREVEPORT RADIOLOGICAL CLUB. *Secretary*, Oscar O. Jones, M.D., 2622 Greenwood Road. Meets monthly September to May, third Wednesday, 7:30 P.M.

Maryland

BALTIMORE CITY MEDICAL SOCIETY, RADIOLOGICAL SECTION. *Secretary*, Harry A. Miller, 2452 Eutaw Place, Baltimore.

Michigan

DETROIT X-RAY AND RADIUM SOCIETY. *Secretary-Treasurer*, E. R. Witwer, M.D., Harper Hospital, Detroit 1. Meetings first Thursday of each month from October to May, at Wayne County Medical Society club rooms.

MICHIGAN ASSOCIATION OF ROENTGENOLOGISTS. *Secretary-Treasurer*, R. B. MacDuff, M.D., 220 Genesee Bank Building, Flint 3.

Minnesota

MINNESOTA RADIOLOGICAL SOCIETY. *Secretary*, C. N. Borman, M.D., 802 Medical Arts Bldg., Minneapolis 2. Regular meetings in the Spring and Fall.

Missouri

RADIOLOGICAL SOCIETY OF GREATER KANSAS CITY. *Secretary*, Wm. M. Kitchen, M.D., 1010 Rialto Building, Kansas City, 6, Mo. Meetings last Friday of each month.

ST. LOUIS SOCIETY OF RADIOLOGISTS. *Secretary*, Edwin C. Ernst, M.D., 100 Beaumont Medical Bldg. Meets on fourth Wednesday of each month, October to May.

Nebraska

NEBRASKA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Ralph C. Moore, M.D., Nebraska Methodist Hospital, Omaha 3. Meetings third Wednesday of each month at 6 P.M. in either Omaha or Lincoln.

New England

NEW ENGLAND ROENTGEN RAY SOCIETY. *Secretary-Treasurer*, George Levene, M.D., Massachusetts Memorial Hospitals, Boston, Mass. Meets monthly on third Friday at Boston Medical Library.

New Hampshire

NEW HAMPSHIRE ROENTGEN SOCIETY. *Secretary-Treasurer*, Albert C. Johnston, M.D., Elliot Community Hospital, Keene. Meetings quarterly in Concord.

New Jersey

RADIOLOGICAL SOCIETY OF NEW JERSEY. *Secretary*, Raphael Pomeranz, M.D., 31 Lincoln Park, Newark 2. Meetings at Atlantic City at time of State Medical Society and midwinter in Newark as called.

New York

ASSOCIATED RADIOLOGISTS OF NEW YORK, INC. *Secretary*, William J. Francis, M.D., East Rockaway, L. I.

BROOKLYN ROENTGEN RAY SOCIETY. *Secretary-Treasurer*, Abraham H. Levy, M.D., 1354 Carroll St., Bklyn. 13. Meets fourth Tuesday of every month, October to April.

BUFFALO RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Mario C. Gian, M.D., 610 Niagara St., Buffalo 1. Meetings second Monday evening each month, October to May, inclusive.

CENTRAL NEW YORK ROENTGEN SOCIETY. *Secretary-Treasurer*, Dwight V. Needham, M.D., 608 E. Genesee St., Syracuse 10. Meetings in January, May, and October.

LONG ISLAND RADIOLOGICAL SOCIETY. *Secretary*, Marcus Wiener, M.D., 1430 48th St., Brooklyn 19. Meetings fourth Thursday evening, October to May, at 8:45 P.M., in Kings County Medical Bldg.

NEW YORK ROENTGEN SOCIETY. *Secretary*, Wm. Snow, M.D., 941 Park Ave., New York 28.

ROCHESTER ROENTGEN-RAY SOCIETY. *Secretary*, Murray P. George, M.D., 260 Crittenden Blvd., Rochester 7. Meets at Strong Memorial Hospital, third Monday, September through May.

North Carolina

RADIOLOGICAL SOCIETY OF NORTH CAROLINA. *Secretary-Treasurer*, James E. Hemphill, M.D., Professional Bldg., Charlotte 2. Meets in May and October.

North Dakota

NORTH DAKOTA RADIOLOGICAL SOCIETY. *Secretary*, Charles Heilman, M.D., 1338 Second St., N., Fargo.

Ohio

OHIO STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Carroll Dundon, M.D., 2065 Adelbert Road, Cleveland 6. Next meeting at annual meeting of the State Medical Association.

CENTRAL OHIO RADIOLOGICAL SOCIETY. *Secretary*, Edward T. Kirkendall, M.D., 700 North Park St., Columbus 8.

CINCINNATI RADIOLOGICAL SOCIETY. *Secretary*, Eugene L. Saenger, M.D., 735 Doctors Bldg., Cincinnati 2. Meets last Monday, September to May.

CLEVELAND RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, George L. Sackett, M.D., 10515 Carnegie Ave., Cleveland 6. Meetings at 6:30 P.M. on fourth Monday, October to April, inclusive.

Oklahoma

OKLAHOMA STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Peter M. Russo, M.D., 230 Osler Building, Oklahoma City. Meetings three times a year.

Oregon

OREGON RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Wm. Y. Burton, M.D., 242 Medical Arts Bldg., Portland 5. Meets monthly, on the second Wednesday, at 8:00 P.M., in the library of the University of Oregon Medical School.

Pacific Northwest

PACIFIC NORTHWEST RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Sydney J. Hawley, M.D., 1320 Madison St., Seattle 4, Wash. Meets annually in May.

Pennsylvania

PENNSYLVANIA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, James M. Converse, M.D., 416 Pine St., Williamsport 8. Meets annually.

PHILADELPHIA ROENTGEN RAY SOCIETY. *Secretary*, Arthur Finkelstein, M.D., Graduate Hospital, Philadelphia. Meets first Thursday of each month at 8:00 P.M., from October to May in Thomson Hall, College of Physicians, 21 S. 22d St.

PITTSBURGH ROENTGEN SOCIETY. *Secretary-Treasurer*, R. P. Meader, M.D., 4002 Jenkins Arcade, Pittsburgh 22. Meets second Wednesday of each month at 6:30 P.M., October to June.

Rocky Mountain States

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Maurice D. Frazer, M.D., Lincoln Clinic, Lincoln, Nebr.

South Carolina

SOUTH CAROLINA X-RAY SOCIETY. *Secretary-Treasurer*, Robert B. Taft, M.D., 103 Rutledge Ave., Charleston 16.

Tennessee

MEMPHIS ROENTGEN CLUB. Meetings second Tuesday of each month at University Center.

TENNESSEE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, J. Marsh Frére, M.D., 707 Walnut St., Chattanooga. Meets annually with State Medical Society in April.

Texas

DALLAS-FORT WORTH ROENTGEN STUDY CLUB. *Secretary*, X. R. Hyde, M.D., Medical Arts Bldg., Fort Worth 2. Meetings on third Monday of each month in Dallas in the odd months and in Fort Worth in the even months.

HOUSTON X-RAY CLUB. *Secretary*, Curtis H. Burge, M.D., 3020 San Jacinto, Houston 4. Meetings fourth Monday of each month.

TEXAS RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, R. P. O'Bannon, M.D., 650 Fifth Ave., Fort Worth 4. Next meeting Jan. 7–8, 1949.

Utah

UTAH STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, M. Lowry Allen, M.D., Judge Bldg., Salt Lake City 1. Meets third Wednesday, January, March, May, September, November.

UNIVERSITY OF UTAH RADIOLOGICAL CONFERENCE. *Secretary*, Henry H. Lerner, M.D. Meets first and third Thursdays, September to June, inclusive, at Salt Lake County General Hospital.

Virginia

VIRGINIA RADIOLOGICAL SOCIETY. *Secretary*, P. B. Parsons, M.D., Norfolk General Hospital, Norfolk 7.

Washington

WASHINGTON STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Homer V. Hartzell, M.D., 310 Stimson Bldg., Seattle 1. Meetings fourth Monday October through May, at College Club, Seattle.

Wisconsin

MILWAUKEE ROENTGEN RAY SOCIETY. *Secretary-Treasurer*, A. Melamed, M.D., 425 E. Wisconsin Ave., Milwaukee 2. Meets monthly on second Monday at the University Club.

RADIOLOGICAL SECTION OF THE WISCONSIN STATE MEDICAL SOCIETY. *Secretary*, S. R. Beatty, M.D., 185 Hazel St., Oshkosh. Two-day meeting in May and one day with State Medical Society, September.

UNIVERSITY OF WISCONSIN RADIOLOGICAL CONFERENCE. Meets first and third Thursdays 4 P.M., September to May, Service Memorial Institute, Madison 6.

Puerto Rico

ASOCIACIÓN PUERTORRIQUEÑA DE RADIOLOGÍA.—*Secretary*, Jesus Rivera Otero, M.D., Box 3524, Santurce, Puerto Rico.

CANADA

CANADIAN ASSOCIATION OF RADIOLOGISTS. *Honorary Secretary-Treasurer*, E. M. Crawford, M.D., 2100 Marlowe Ave., Montreal 28, Quebec. Meetings in January and June.

LA SOCIÉTÉ CANADIENNE-FRANÇAISE D'ELECTROLOGIE ET DE RADIOLOGIE MÉDICALES. *General Secretary*, Origéne Dufresne, M.D., Institut du Radium, Montreal. Meets third Saturday each month.

CUBA

SOCIEDAD DE RADIOLOGÍA Y FISIOTERAPIA DE CUBA. Offices in Hospital Mercedes, Havana. Meets monthly.

MEXICO

SOCIEDAD MEXICANA DE RADIOLOGÍA Y FISIOTERAPIA. *General Secretary*, Dr. Dionisio Pérez Cosío, Marsella 11, México, D. F. Meetings first Monday of each month.

ABSTRACTS OF CURRENT LITERATURE

ROENTGEN DIAGNOSIS

The Head and Neck

The Chest

The Digestive System

The Adrenal Glands

The Musculoskeletal System

The Genito-Urinary System

RADIOTHERAPY

RADIATION EFFECTS

ROENTGEN DIAGNOSIS

THE HEAD AND NECK

Cranial Laminagraphy. Enzo Bullo. Radiol. med. (Milan) **33:** 273–284, June 1947.

The author discusses the peculiarities of the laminagraphic technic when applied to the skull. He explains the limitations of the unidirectional laminagraph and its peculiar disadvantages in skull work, but does not mention that these disadvantages disappear when one employs other types of laminagraphy, such as the spiral laminagraph advocated by Kiefer and Moore (Am. J. Roentgenol. **39:** 497, 514, 1938).

CESARE GIANTURCO, M.D.

Plesioradiography of the Temporal Bone. Ferdinando Carini. Radiol. med. (Milan) **33:** 292–296, June 1947.

Plesiography is a type of radiography involving an extremely short focal distance, the purpose being to eliminate the images of objects close to the tube while obtaining sharp images of those close to the film. Plesiography can be used to good advantage in radiography of the mastoids, temporomandibular joints, or sternoclavicular joints by placing the tube close to the skin on the opposite side of the body and the film in contact with the part to be studied. The author presents beautiful roentgenograms of the temporal bone taken with this technic. CESARE GIANTURCO, M.D.

Symmetric Cerebral Calcification Which Followed Postoperative Parathyroid Insufficiency: Report of a Case. Irving S. Siglin, L. M. Eaton, John D. Camp and Samuel F. Haines. J. Clin. Endocrinol. **7:** 433–437, June 1947.

The occurrence of cerebral calcification has been demonstrated roentgenographically in 11 of 17 patients with spontaneous parathyroid insufficiency studied at the Mayo Clinic from 1935 through 1945. A case is now reported in which symmetric cerebral calcification was associated with parathyroid insufficiency developing after thyroidectomy. The authors believe this case supports the opinion that the characteristic cerebral pathologic process actually is secondary to parathyroid insufficiency, and that the cerebral changes are not the cause of the disturbance. The intermittency of symptoms in this instance was similar to that frequently seen in cases of postoperative parathyroid insufficiency. Adequate treatment of the parathyroid insufficiency leads to relief of clinical symptoms, including convulsions, but does not cause the cerebral calcification to disappear. Roentgenograms are reproduced.

THE CHEST

Bronchial Occlusion in Childhood Tuberculosis: Its Pathogenesis and Effects. James H. Hutchison. Edinburgh M. J. **54:** 322–324, June 1947.

The author advances the theory that the extensive shadows seen in roentgenograms of children with primary tuberculous infection are due to the presence of absorption collapse produced by bronchial occlusion and do not indicate pneumonic consolidation, as commonly believed. The occlusion of the bronchus is most often caused by extrinsic pressure of enlarged tuberculous lymph nodes on the bronchial wall, sometimes in combination with sticky mucus from a swollen hyperemic membrane. In some cases a caseous tuberculous node adheres to the bronchial wall and ulcerates into the lumen with the production of granulation tissue therein.

Although the diagnosis of tuberculous infection can be confirmed in every patient by tuberculin skin tests, clinical signs rarely permit an accurate diagnosis of absorption collapse. In only 19 of a series of 45 cases were local signs, such as percussion note, diminished air entry, bronchial breath sounds, and scanty râles, detected. In 5 cases only was there evidence of mediastinal shift to the affected side. In 15 cases there was a history of asthma-like or wheezy breathing or of spasms of nocturnal coughing with respiratory distress, and this is regarded as evidence of bronchial occlusion.

Roentgen signs of collapse are not, as a rule, difficult to recognize, although they are frequently mistaken for consolidation. The right upper or middle lobes are most frequently affected; next in frequency, the left upper and lower lobes. Evidence of mediastinal or tracheal shift to the affected side was found roentgenologically in 17 of the 45 cases. Elevation of the diaphragm or "crowding" of the ribs was not seen in any case. The author attributes the comparative infrequency of these signs of collapse to the fact that when the bronchial lumen is occluded gradually, and especially if parenchymal tuberculosis is present in the affected lobe or sector, the outpouring of fluid into the tissues may be more rapid than the absorption of air, so that the volume of the lobe may be as great or actually greater than that of the normal lobe.

Partial obstruction by extrinsic pressure associated with a swollen hyperemic mucous membrane may allow entry of air to the alveoli distal to the site of the bronchial narrowing during inspiration, when the bronchi normally dilate slightly; during expiration, the slight narrowing of the bronchus may result in complete obstruction at the narrowed part of the lumen so that the exit of air cannot take place, causing ballooning of the air-spaces or obstructive emphysema.

Apical Scars. Their Etiological Relationship to Tuberculous Infection. E. M. Medlar. Am. Rev. Tuberc. **55:** 511–516, June 1947.

The author's studies of autopsy material obtained from persons dying unexpectedly revealed apical scars in 44.1 per cent of 960 white persons and 12 per cent of 299 Negroes. None was observed in 106 individuals under twenty years of age. Apical scars were present with equal frequency in persons who exhibited no macroscopic evidence of tuberculosis in their tissues and in those having single or multiple foci. These findings and others discussed by the author lead him to believe that typical bilateral apical scars, sometimes called "apical caps," are not etiologically related to tuberculous infection. Since significant tuberculosis may occur in the same location, it becomes necessary to differentiate, if possible, between these two conditions. Inasmuch as apical scars occur rarely below the age of thirty, they need not be considered in that age group even in the presence of bilateral apical shadows.

The increasing frequency of bilateral apical scars with advancing age indicates the necessity for caution in the

interpretation of apical shadows as tuberculous, especially in white males over fifty years of age. The problem is less complicated in the Negro, for bilateral apical scars, non-tuberculous in nature, were found infrequently at any age in that race. Since tuberculous lesions in association with apical scars are more often unilateral than bilateral, a considerable inequality of the shadows on the two sides would suggest a tuberculous lesion. L. W. PAUL, M.D.

Lung Calcifications and Histoplasmin-Tuberculin Skin Sensitivity. L. W. Sontag and John E. Allen. J. Pediat. **30:** 657–667, June 1947.

As part of the Fels Research Institute (Antioch College) study of 200 normal children from Southwestern Ohio, including chest films from birth, the relationship of skin-sensitivity tests to lung calcifications has been investigated. For this purpose, 170 children one year of age and over were tested with tuberculin and histoplasmin.

Of the group examined, 60.6 per cent showed pulmonary calcifications. A positive reaction to tuberculin (Purified Protein Derivative) was obtained in 15.3 per cent, while 44 per cent reacted positively to histoplasmin. The study showed an increase in positive tuberculin reactions with age, reaching a maximum of 40.9 per cent in the fifteen- to nineteen-year-old group, by which time the incidence of calcification was between 90 and 95 per cent. Histoplasmin reactions reached a peak of 64 per cent in children between ten and fourteen and maintained approximately the same level between fifteen and nineteen. The incidence of pulmonary calcification with negative tuberculin and histoplasmin tests changed little after the age of five.

It was also shown that the onset of pulmonary calcification exceeded the development of histoplasmin sensitivity. This is assumed to be due either to a lag of calcification or the occurrence of calcifications from causes other than histoplasmosis. This latter assumption was borne out by observations in 33 children who reacted neither to tuberculin or histoplasmin. These children were tested with haplosparangin and blastomycin. One child reacted to haplosparangin and two to blastomycin.

The authors state that parenchymal lesions occur much more frequently in the bases than in the apices of the lungs. The pre-calcific lesions varied from fuzzy, fan-shaped extensions and exaggerations of linear markings, running into the periphery, to round areas of definite consolidation, often 2.5 cm. or more in diameter. These appear as early as the eleventh to the twenty-fourth month of life. They show beginning calcification in twelve to fifteen months and are heavily calcified in two to three years. Calcification of the hilar nodes draining such initial lesions often does not occur until two and a half years or more after the parenchymal lesions calcify. The authors feel that the process is often a progressive one, showing new soft-tissue lesions and additional areas of both parenchymal and hilar calcification over a period of six years. Calcifications may occur as early as the first year of life.

No definite criteria were recognized to distinguish between the calcification pattern of tuberculosis and that of histoplasmosis, but it is felt that histoplasmosis has a tendency to show the following features: (1) multiple areas in the parenchyma; (2) early onset, frequently before one year of age; (3) preceding pneumonic infiltrate early in the infection; (4) progression, with development of new lesions and calcification over a period of years. It is therefore concluded that there is much closer association between the onset of calcification and the development of histoplasmin sensitivity than between calcification and the development of tuberculin sensitivity. It is thought that the histoplasmosis organism may remain active in the body for many years. A tendency for familial distribution of lung calcifications was noted, but this did not hold for positive histoplasmin reactions. It is re-emphasized that a far greater number of children are sensitive to histoplasmin than to tuberculin. J. C. FURNARI, M.D.

Tuberculosis in Discharged Soldiers. William Porter Swisher. Am. Rev. Tuberc. **55:** 481–487, June 1947.

Among 196,000 soldiers who had chest roentgenograms at the time of their discharge, active pulmonary tuberculosis was found in 175 (0.88 per thousand). Pre-induction films were available for comparison in 62 instances and about one-half of these revealed shadows which should have been investigated at the time. An additional 20 soldiers were found to have arrested tuberculosis.

These low rates are compared to those reported among civilians at the time of induction, namely, 3 to 15 cases per thousand examinations. They indicate the value of mass surveys in helping to eradicate tuberculosis from the population. L. W. PAUL, M.D.

Use of Electro-Shock Therapy in Psychiatric Illness Complicated by Pulmonary Tuberculosis: Report of a Case. Otto Allen Will, Jr., and Addison M. Duval. J. Nerv. & Ment. Dis. **105:** 637–646, June 1947.

A case is presented in which an apparently latent pulmonary lesion in a patient with schizophrenia became markedly active shortly after the completion of electroshock therapy. Roentgenograms of the chest on Sept. 8, 1944, revealed a "moderately advanced" lesion in the right upper lobe. No clinical evidence of active tuberculosis was found with the exception of an elevated erythrocyte sedimentation rate (33 mm. in one hour). Repeated gastric washings were negative for acid-fast organisms. Because of the x-ray findings, shock therapy was deferred, but was considered again as the patient became increasingly depressed, and at times agitated and suicidal. A roentgenogram on October 24 showed at the level of the first interspace, on the right side, a shadow definitely indicating a moderately advanced tuberculous infection. Therapy was again delayed, but during nearly two months of further observation there was no clinical evidence of active tuberculosis and the patient continued to gain weight.

Eight electroshock treatments were given between Dec. 21, 1944, and Jan. 6, 1945, curare being used to reduce the severity of the convulsion on only one occasion. The patient's mental condition improved, but about two weeks after the last treatment it was noticed that he was eating poorly and complained of fatigue. Physical examination disclosed the presence of fine râles at the right apex, beneath the right scapula, and in the right midaxillary region. A chest film on Jan. 23 showed a decided increase of density in the right upper lobe and a slight increase in the left upper lobe. The patient's condition became progressively worse and he died in December 1945.

Case of Massive Conglomerate Tuberculosilicosis Simulating Pulmonary Neoplasm. Warriner Woodruff and Winfield O. Kelley. J. Thoracic Surg. **16:** 282–290, June 1947.

A 58-year-old male had rather minimal evidences of silicosis in the lungs, plus a large, well defined mass at the right base posteriorly and medially. Since it was believed that this might be a neoplasm, a pneumonectomy was done, with complete recovery. The specimen showed a diffuse silicosis, the large mass proved to be a typical conglomerate silicotic lesion with caseation, and an occasional acid-fast bacillus was found. Eight cases reported in the literature are cited briefly.

The authors feel that in the presence of known silicosis a large nodule or mass in the lung is more likely to represent silicosis than neoplasm. They believe, however, that surgery may be justified, since one cannot clearly exclude a new growth. Sometimes, also, the large conglomerate nodules cavitate and this can be avoided by removal. HAROLD O. PETERSON, M.D.

Bronchography in Bronchiectasis in Children. D. E. Staunton Wishart. Ann. Otol., Rhin. & Laryng. **56:** 404–415, June 1947.

Bronchography is of vital significance to the surgeon about to deal with a bronchiectatic lung. The importance of the procedure in children is indicated by statistics from the Hospital for Children in Toronto, showing, since 1944, 28 lobectomies and 5 pneumonectomies in patients under fourteen years of age. While in co-operative children of thirteen or fourteen, the bronchial tree can eventually be completely mapped by the adult catheter technic, as recommended by Jackson and Bonnier (Ann. Otol., Rhin. & Laryng. **46:** 771, 1937), the present author prefers the bronchoscopic method, having overcome certain objections to that procedure by carrying it out in its entirety on the fluoroscopic table in the x-ray department under general anesthesia.

As performed by the author and his associates, bronchography is usually completed in two delineations. A bronchogram of one lung at a time is obtained, the patient's body being moved into various positions and roentgenograms being taken in each of these to insure complete mapping. With the bronchoscope in position, the body can be turned at will, even face down, without danger of trauma if proper care is exercised.

The maintenance of a long, quiet, even anesthesia is difficult but essential. Upon this the success of the procedure depends to a greater extent than upon any other factor. Ether, vaporized by an oxygen current, is delivered through a rubber tube attached to the anesthetic arm of the bronchoscope. To maintain the anesthesia, thin-walled metal intubation tubes have been found most satisfactory.

The technic of the procedure is described in some detail. The successive steps are: (1) induction of anesthesia; (2) suction aspiration of the bronchial tree through the bronchoscope; (3) insertion of special intubation tubes for maintenance of anesthesia; (4) insertion of a small catheter into the bronchial tree; (5) injection of iodized oil: (6) spot films (Bucky diaphragm not used); (7) large films (with Bucky). The cough reflex starts working immediately after the operation is over and is an important factor in the invariably rapid recovery.

The right lung is mapped first, and an interval of several weeks is allowed to elapse before study of the second lung is undertaken. The main consideration is that most of the oil injected previously shall have vanished so that delineation of the left bronchial segments is not impaired by overlying iodized oil in parts of the right lung. STEPHEN N. TAGER, M.D.

An Unusual Pulmonary Disease. James C. Cain, Edward J. Devins, and John E. Downing. Arch. Int. Med. **79:** 626–641, June 1947.

Twenty-six cases of an unusual pulmonary disease occurred late in March 1944 in eastern Oklahoma. The one proved common factor among these cases is that each man who contracted the disease had spent some time in an abandoned storm cellar on the military reservation at Camp Gruber, Okla. The men were from two companies living in different camp areas, used separate messes, and had never previously trained together. Every fifth man from the two companies involved was questioned and a roentgenogram of the thorax was made. Chest films in 100 cases of primary atypical pneumonia and tuberculosis occurring during this period were not similar to those of the affected men.

The onset of symptoms was sudden, characterized by general malaise, fatigue, and muscular aching, followed within twenty-four to thirty-six hours by a chill (or chilliness), high remittent temperature, sweating, constricting pain in the thorax, and epistaxis. Examination of the thorax revealed a striking paucity of clinical signs. Laboratory studies yielded little of significance. Roentgenograms of the chest were characterized by numerous small areas of infiltration, from 1 to 20 mm. in diameter, scattered diffusely and symmetrically throughout the fields of both lungs except for a tendency to spare the apexes and bases. In all cases the hilar lymph nodes were enlarged. These conditions were apparent a few days after the clinical onset of the disease and reached a maximal intensity within ten to twelve days. The mottled infiltrations remained static for about two months, after which time resolution became apparent. As the areas diminished in size, they became more discrete and fibrotic, and by the sixth month the pulmonary fields showed a diffuse, fine fibrosis. From then on, further change was imperceptible, and the fibrosis was considered to be permanent. The reduction in size of the hilar nodes to normal or near normal paralleled the decline of the infiltrated areas.

The sudden onset, the severe and prolonged clinical course, and the disseminated lesions seen roentgenologically differentiated this disease from primary atypical pneumonia. Psittacosis was considered, but the absence of any history of exposure to birds, the lack of evidence of large areas of pulmonary consolidation in the roentgenograms, the negative results of complement-fixation tests, and the fact that all the patients recovered fail to support this diagnosis. The sera of 10 patients were negative for Q fever. Serologic tests for histoplasmosis were also negative. The diagnosis of coccidioidomycosis was excluded by the occurrence outside of a recognized endemic region, the absence of cavitation, or of secondary dissemination in any case, and the negative reactions to coccidioidin tests. Although *C. albicans* was found in the sputum of 16 patients, due to the lack of supporting immunologic evidence it is questionable that this organism was the cause of the disease. These cases most closely resemble those described by Idstrom and Rosenberg (Bull. U. S. Army M. Dept., October 1944, No. 81, pp. 88–92), which were classified as primary atypical pneumonia.

Five similar cases occurred at Camp Gruber in February 1943.

Benign Mediastinal Tumors: Report of Six Cases with Analysis of Diagnostic Criteria and Advocation of Surgical Removal. Esther Silveus and Ralph Adams. Surg. Clin. North America **27:** 596–604, June 1947.

Six cases illustrating the four most commonly encountered types of mediastinal tumor are reported: (1) a dermoid cyst; (2) teratoma: (3) bronchial cyst; (4) neurofibroma; (5) ganglioneuroma; (6) neurofibromatosis. The criteria for diagnosis are reviewed, and adequate illustrations are included. It is pointed out that in a series of 288 cases of dermoid cyst and teratoma reviewed by Laipply (Arch. Path. **39:** 153, 1945) 28 or 11.4 per cent were malignant.

The authors believe that for adequate demonstration of these tumors the roentgen examination should include fluoroscopy with barium in the esophagus, posteroanterior stereoscopic films, a lateral film, and a film to record bony detail. The presence or absence of calcification may well be a deciding factor in the diagnosis and should be carefully sought. Tooth-like vestiges are, of course, diagnostic of a dermoid. A skin test with echinococcus antigen is useful in some cases.

SYDNEY F. THOMAS, M.D.

Neurofibroma of the Posterior Mediastinum. I. Darin Puppel. Surgery **21:** 875–880, June 1947.

The only real danger in not removing neurogenic mediastinal tumors lies in the possibility of malignant change. With modern technics, removal is relatively simple and mortality rates are low.

The case reported is that of a 61-year-old white man, with a diagnosis of cardiac disease and intrathoracic tumor made in 1941. Initial symptoms were mild intermittent dyspnea and occasional choking sensation especially when the patient lay on the right side. Roentgen therapy was instituted on the basis that surgery would be dangerous, but the tumor proved radioresistant and treatment was discontinued. During the next four years, the patient complained mostly of symptoms arising from worry over his condition. In June 1945, roentgenograms demonstrated no change in the appearance of the intrathoracic mass. A diagnosis of probable benign tumor of neurogenic origin was made. Preoperative antibiotic therapy was given, and thoracotomy was done, with removal of the encapsulated tumor. Recovery was uneventful.

The tumor was 6 cm. in diameter and weighed 60 gm. The pathological diagnosis was neurofibroma. The patient was symptom-free twelve months after operation.

JOHN E. WHITELEATHER, M.D.

Spontaneous Mediastinal Emphysema with Acute Right Ventricular Strain. Arthur Klein. Am. Heart J. **33:** 867–874, June 1947.

A case is reported of spontaneous mediastinal emphysema with acute right ventricular strain in a 16-year-old Negro boy. The patient suffered from bronchial asthma, and the more recent asthmatic attacks were associated with upper respiratory infections.

Features characteristic of spontaneous mediastinal emphysema are: precordial and substernal pain in a healthy person, or occasionally in one with a history of asthma; a crunching sound over the precordium; roentgen demonstration of air in the mediastinal tissues. The condition may follow trauma to the chest, stresses of various respiratory diseases in childhood, and positive-pressure intratracheal anesthesia.

The mechanism of the development of spontaneous mediastinal emphysema, as described by Macklin in various papers (see, for example, Medicine **23:** 281 1944), is hyperinflation of alveoli, leakage and escape of air along the perivascular sheaths of the pulmonary vessels in blebs of increasing size toward the hilum, and rupture into the mediastinum. The pulmonary interstitial emphysema encroaches upon the space occupied by the pulmonary vessels, interferes with the circulation through the lung, and may result in embarrassment to the right heart.

The author gives the characteristic EKG findings in acute right ventricular strain and includes the roentgenograms and EKG tracings of the case which he reports.

HENRY K. TAYLOR, M.D.

Congenital Malposition of the Aortic Arch. Double Arch and Right-Sided Aorta. C. Patiño Mayer, Luis Lepera, Francisco A. Pataro, and Hector Quereilhac. Radiología (Buenos Aires) **8:** 151–165, May–December 1945.

The authors enter first into a discussion of the embryologic development of the normal aorta, following the description of Arkin and others. After a lengthy account of the basic embryologic and anatomical considerations, they record a case which proves authoritatively that the anomaly of a right-sided aorta can exist without any symptoms whatever to denote its presence at least until advanced age, in which, as a consequence of elongation and dilatation of the vessels, there may occur the phenomenon of compression of the trachea and esophagus, as was true in their patient.

The authors present an extensive review of the subject, including angiocardiographic studies. They conclude that when angiocardiography is not feasible, kymography is of incalculable value for differential diagnosis. The bibliography is extensive.

JAMES T. CASE, M.D.

THE DIGESTIVE SYSTEM

Spontaneous Rupture of the Esophagus. Report of a Case with Recovery. Norman William Frink. J. Thoracic Surg. **16:** 291–297, June 1947.

Spontaneous rupture of the esophagus is of rare occurrence. Though it is generally accepted to be fatal, the patient reported in this paper recovered.

A review of the literature in 1943 disclosed 40 cases with 100 per cent mortality. Most commonly the patient is a male, between thirty-five and forty-five years of age, who has been a heavy drinker. After an episode of forceful vomiting with or without hematemesis he is seized suddenly with agonizing upper abdominal or substernal pain. There may be a transient subcutaneous emphysema in the neck and upper anterior chest wall. Soon there is a left hydrothorax or hydropneumothorax. In a few hours the patient goes into vascular collapse, from which he rarely recovers. A swallow of barium with films or fluoroscopy is the best way of making the diagnosis. Treatment is probably largely supportive, plus antibiotics. The advisability of immediate surgery and closure of the tear is a debatable matter. In the case reported here recovery was gradual and the fistula healed spontaneously following open thoracotomy for drainage of the empyema. Massive hemor-

rhage may occur. Late strictures may develop if the patient survives. HAROLD O. PETERSON, M.D.

A Method for Determining the Effect of Various Agents on Gastric Evacuation in Man. J. H. Annegers and A. C. Ivy. Gastroenterology **8:** 711–716, June 1947.

The usual roentgenological method of studying gastric evacuation is to administer a heavy barium meal and to estimate the rate of emptying from serial examinations. This method is suitable for detecting individual differences in rate of gastric evacuation, but is poorly adapted to the determination of the effects of variation in composition of a meal on its rate of evacuation, since the barium suspension itself is the principal component of the meal.

The authors present a method for determining changes in the rate of evacuation from the stomach of test meals of any desired composition. The method does not interfere with physiologic gastric motor and secretory activity.

After normal gastric evacuation has proceeded for several hours following a mixed meal, a small amount of barium suspension is given, a film is immediately exposed, and the area of the projected x-ray shadow is measured with a planimeter. The area of this shadow depends upon (*a*) the volume of the gastric contents and (*b*) the geometric configuration of the stomach. Individual differences in stomach configuration prevent detection of abnormal individual differences in gastric evacuation. For a given individual, however, it has been found that the area of the projected x-ray shadow remains remarkably constant upon repeated tests when the fasting stomach is filled with a given volume of barium suspension. This consistency enables determination in a given subject of the relative rates of evacuation of meals of different composition. Each subject thus serves as his own control.

M. WENDELL DIETZ, M.D.

Extramucosal Tumors Simulated by Gastric Carcinoma. Robert M. Lowman, Robert Shapiro, and Samuel D. Kushlan. Am. J. Roentgenol. **57:** 726–735, June 1947.

In an excellent critical evaluation the authors review the points of diagnostic value in differentiating between gastric carcinoma and extramucosal intramural masses. They feel that neither the location nor the presence or absence of central ulceration is of value in distinguishing between benign and malignant growths.

Three cases of adenocarcinoma of the stomach are reported, their appearance fulfilling all of the roentgen criteria set forth in the literature for the diagnosis of extramucosal tumors. These tumors appeared to be smooth, well defined, and circumscribed. In the first and third cases, however, a coarse, irregular, reticular pattern of the surface was noted on mucosal relief films. In these cases the abnormal changes were caused by irregular mucosal and submucosal proliferation and infiltration by tumor cells alone in some areas, while there was a marked associated inflammatory reaction in others.

The authors indicate that the presence of the reticular pattern would mitigate against the diagnosis of a benign lesion because the submucosal infiltration in such tumors is regular and sharply circumscribed. The one possible exception to this is the rare occasion of tumefactive localized polypoid hypertrophic gastritis as reported by Hinkel (Am. J. Roentgenol. **53:** 20–27 1945). ELLWOOD W. GODFREY, M.D.

Supradiaphragmatic Section of the Vagus Nerves to the Stomach in Gastrojejunal Ulcer. Lester R. Dragstedt, James S. Clarke, Paul V. Harper, Jr., Edward R. Woodward, and E. Bruce Tovee. J. Thoracic Surg. **16:** 226–236, June 1947.

Ten cases are reported in which vagotomy was done for gastrojejunal ulcer following gastro-enterostomy or partial gastrectomy. Uniformly good results were obtained, as shown by relief of distress and fluoroscopic demonstration of disappearance of large ulcer craters. A résumé of the rationale of treating peptic ulcer by vagotomy is given. It is based chiefly on the reduction in the amount of gastric secretion, particularly at night, and a decrease in the degree of acidity. That relief of pain is not due to an anesthetic effect through removal of the sensory nerve supply of the stomach is indicated by the immediate reappearance of typical pain when acid is instilled into the stomach during the first few days following operation.

Division of the vagus nerve supply to the stomach may be accomplished either by a supradiaphragmatic or a subdiaphragmatic route. The former was used in the cases reported in this paper, but good results have also been achieved with the latter. Each has certain advantages.

[The subject of vagotomy in peptic ulcer was reviewed editorially in Radiology **49:** 97, 1947.]

HAROLD O. PETERSON, M.D.

Jejunal Malignancy. Earl A. Connolly and Arnold W. Lempka. Surgery **21:** 901–910, June 1947.

The rarity of malignant growths of the small bowel is evident from a study of the literature. While the prognosis is in general poor, the authors record two cases with survivals of five years and six and a half years, respectively, after resection.

Most of the patients are of middle age. Symptoms are variable and vague. Nausea and vomiting due to obstruction have been seen; hemorrhage may occur, and anemia may develop. Weakness, loss of weight, dizziness, and fatigue are common. With a narrowed lumen, there may be pain and distention. Constipation may alternate with diarrhea. A lesion protruding into the lumen can give rise to intussusception.

Roentgen findings include: (1) a filling defect in the lumen; (2) small bowel dilatation proximal to the obstruction; (3) retention of barium proximal to the lesion; (4) signs of avitaminosis, sprue, pellagra, and hypoproteinemia. The greatest value of the roentgen examination is in the demonstration of a narrowing of the lumen with obliteration of the mucosal folds.

A definite diagnosis can be made only by roentgenography, laparotomy, or autopsy, but not more than 25 per cent of the lesions are demonstrable by the most skilled roentgenologists. Differentiation from inflammatory lesions must be made. Generally, malignant constrictions are short, 2 to 4 cm. in length, while inflammatory lesions usually extend along the intestine for at least 8 to 10 cm.

Adenocarcinomas comprise the majority of malignant growths of the jejunum. Leiomyosarcoma and epithelioma have been seen.

The authors' first patient was originally seen in 1932

at the age of forty and was treated repeatedly for bleeding duodenal ulcer. In 1941 a mass had become palpable in the right abdomen. This was resected with 12 cm. of jejunum. The tumor, 6 cm. in diameter, arose from the antimesenteric border. There was a diverticulum into the mass, with evidence of hemorrhage. Diagnosis was polypoid subserous leiomyosarcoma, grade I.

The second patient, a 47-year-old woman, complained of paroxysmal abdominal pain and frequent vomiting for six months, a vague feeling of suffocation, and loss of weight. Roentgen examination showed a nearly complete obstruction of the upper jejunum, with severe dilatation and retention of barium proximal to the obstruction for twenty-four hours. At operation, a firm, annular constricting growth was found 12 inches from the ligament of Treitz and was resected. The pathological diagnosis was papillary adenocarcinoma, grade II.

JOHN E. WHITELEATHER, M.D.

Prognosis of Patients with Carcinoma of the Colon, Rectosigmoid and Rectum. Frank H. Lahey. Surg. Clin. North America **27:** 670–674, June 1947.

The author believes that the diagnosis of carcinoma of the colon and rectum can usually be made from the history, particularly as to (1) the presence of blood in the stools, (2) obstructive pain, (3) alteration of bowel function, and (4) change in the caliber of the stools. Upon the basis of these features and the roentgenologic findings it is often possible to make quite an accurate prognosis as to the extent of the lesion, its operability, and the likelihood of recurrence. When any one of the four symptoms mentioned has been present for a period of months, it is reasonable to assume that the lesion is late and therefore must belong to a less favorable group.

The roentgen findings which are of particular prognostic significance are annularity and canalization. An annular growth suggests a duration of at least six months, since it takes that time for a lesion to spread from its point of origin on the bowel wall to involve the entire circumference. When, in addition, it can be shown that the carcinoma has canalized the bowel by growing along it, a duration of six months to a year may be assumed. These findings, however, even with a long history of symptoms, should not discourage exploration, but should rather serve merely in prophesying for one's own benefit the operability in any given case. The unpredictable behavior of these tumors as to rapidity of growth and metastasis is well known.

Special mention is made of anemia, and it is pointed out that with involvement of the right colon unexplained secondary anemias may produce evidence of cachexia which is by no means indicative of inoperability, though it would certainly have that significance were the lesion in the left colon.

SYDNEY F. THOMAS, M.D.

Importance of Malignant Degeneration as a Complication of Chronic Ulcerative Colitis. Richard B. Cattell and Earl J. Boehme. Gastroenterology **8:** 695–710, June 1947.

The frequency with which chronic ulcerative colitis predisposes to the development of cancer is not well recognized. This paper adds to the reported cases of ulcerative colitis undergoing malignant change (approximately 75) 9 more seen in the Lahey Clinic in a seven-year period.

The chief reason for the comparatively few cases recorded in the literature is that long follow-up studies are necessary. In this series the average interval from the onset of ulcerative colitis until the development of the cancer was over nine years. In a series of 54 cases studied at the Mayo Clinic it was 17.6 years (Bargen and Sauer: Clinics **3:** 516, 1944). During such a long interval many cases are not traceable. It is probable that some patients die of carcinoma when the ulcerative colitis is in complete remission. The death is thus not associated with the previous condition or it is attributed to a reactivation of the colitis. Another factor entering into consideration is the large number of cases of ulcerative colitis which are not operated on. In addition, some of the patients who have died with ulcerative colitis without necropsy probably actually had cancer.

Carcinoma arising on colitis is highly malignant and metastasizes early. Few patients have had resections and only an occasional one has survived five years. Periodic roentgenographic and sigmoidoscopic study of the colon is indicated in all cases of long-standing ulcerative colitis in which colectomy has not been required or in which the colon has been defunctionalized by ileostomy. So-called cured cases should also be reexamined at regular intervals.

M. WENDELL DIETZ, M.D.

Large Diaphragmatic Hernia Without Symptoms. Report of Two Cases. Martin G. Goldner and Jack H. Levy. Gastroenterology **8:** 788–792, June 1947.

Although extensive diaphragmatic hernias are not uncommon, the cases herein presented are unusual because of the marked discrepancy between the signs and symptoms. In each case, large parts of the abdominal contents were situated in the thorax, yet the condition was completely asymptomatic in one and caused only minimal symptoms in the other. In both instances the condition was discovered upon routine physical examination. Roentgenologically, both herniations appeared to occur through the pleuro-peritoneal hiatus.

Surgical repair was considered too dangerous a procedure to be attempted during the asymptomatic phase of these cases, although serious risk of incarceration or obstruction is recognized.

M. WENDELL DIETZ, M.D.

THE ADRENAL GLANDS

Roentgenographic Delineation of the Adrenal Glands with the Aid of Laminography. Seymour F. Wilhelm. Brit. J. Urol. **19:** 85–89, June 1947.

In a series of 44 perirenal insufflations, laminagrams proved far superior to simple films in delineating the normal adrenal gland and its lesser enlargements. The laminagraphic technic affords accurate information as to the presence, size, and shape of the contralateral adrenal shadow, thus obviating the necessity of bilateral surgical exposure in patients undergoing adrenalectomy. The shadows of the normal adrenal gland are usually seen most distinctly at a level of 7 to 9 cm. above the table top.

Illustrative case reports include instances in which normal adrenal shadows contraindicated surgical exploration and one in which laminagraphy showed considerable circular enlargement of the gland with calcification. In this latter case pathological examination showed a neurocytoma.

M. WENDELL DIETZ, M.D.

THE MUSCULOSKELETAL SYSTEM

Differential Diagnosis of Cystic Lesions of Bone. James W. Toumey. Surg. Clin. North America **27:** 737–754, June 1947.

The scope of this article is wider than the title implies, as is obvious from the list of cystic lesions of bones which the author has included:

- Osteomyelitis
- Brodie's abscess or bone abscess
- Fibrous dysplasia or osteitis fibrosa cystica or fibrocystic disease
  - Bone cyst or latent or solitary bone cyst
  - Polyostotic fibrous dysplasia (von Recklinghausen)
  - Hyperparathyroidism
  - Albright's syndrome
- Osteitis deformans or Paget's disease
  - Monostotic Paget's disease
- Bone tumors
  - Osteogenic sarcoma
    - Medullary and subperiosteal
    - Telangiectatic
    - Sclerosing
    - Periosteal
    - Fibrosarcoma
      - Medullary
      - Periosteal
    - Parosteal, capsular
  - Chondroma series
    - Chondrosarcoma
    - Myxosarcoma
    - Chondroma
  - Giant-cell tumor series
    - Malignant
    - Epiphyseal giant-cell tumor (benign)
  - Angioma series
    - Angio-endothelioma
    - Diffuse endothelioma or Ewing's tumor
    - Cavernous angioma
    - Plexiform angioma
  - Myeloma series
    - Plasma-cell (common form or multiple myeloma)
    - Myelocytoma
    - Erythroblastoma
    - Lymphocytoma
  - Reticulum-cell lymphosarcoma
  - Liposarcoma
  - Metastatic malignancy
    - Breast
    - Prostate
    - Thyroid
- Xanthomatosis
- Syphilis
- Tuberculosis
- Eosinophilic granuloma of bone
- Lymphoblastoma or lymphoma
  - Hodgkin's disease
- Leukemia
  - Chloroma
- Osteoid osteoma
- Echinococcus of bone

Many of the lesions illustrated appear to be far from cystic, but considerable detail may have been lost in the reproduction. The article tries to be too inclusive and thereby includes many entities which are rarely cystic. The illustrations are, however, worth reviewing and the bibliography is extensive.

SYDNEY F. THOMAS, M.D.

Extramedullary Spinal Cord Tumors. Gilbert Horrax. Surg. Clin. North America **27:** 535–553, June 1947.

It is implied in this paper that patients suffering from extramedullary spinal cord tumors are likely to be late in reaching the neurosurgeon because of failure to recognize any of the early signs. It is obvious that in the author's view the most important part of the examination is a careful neurologic study, which may be supplemented by roentgenography and spinal fluid studies. If the level of the lesion cannot be determined by the neurologic examination, roentgen studies with lipiodol or pantopaque are indicated unless there is a complete fluid block, in which event oxygen or air spinograms are preferable.

Since 1932, 141 spinal cord tumors have been verified at operation or autopsy at the Lahey Clinic. Of this number, 53 (37.5 per cent) have been benign extramedullary growths, either neurofibromas or meningiomas. From this group examples of tumors in various regions of the spine have been selected to illustrate the symptomatology.

Two cases of extramedullary *cervical* tumors are reported. One of these exemplified root pain without general signs of cord compression of any degree. A myelogram with lipiodol showing a definite filling defect at C-7 is reproduced. An interesting feature of the second case was the disappearance of pain on lying down and its return in the upright position, which is the reverse of the usual observation in the presence of a spinal cord tumor. Spinal puncture produced an aggravation of the symptoms. Lipiodol studies are said to have shown complete block at the level of the seventh cervical vertebra, but the films are not reproduced.

In the *thoracic* region, extramedullary tumors tend to produce root pain according to the level involved. Tumors at the upper levels may simulate cardiac or shoulder disease, while in the lower thoracic region upper abdominal acute conditions must be differentiated. Three cases are presented, with reproductions of myelograms in two.

Two examples of tumors in the *lumbar* region are described and an oxygen spinogram from one case is reproduced.

SYDNEY F. THOMAS, M.D.

Low Back Pain Associated with Varices of the Epidural Veins Simulating Herniation of the Nucleus Pulposus. Bernard S. Epstein. Am. J. Roentgenol. **57:** 736–740, June 1947.

The author reports three cases presenting a history and findings typical of herniation of the nucleus pulposus at the lumbosacral level. In two instances further confirmation was obtained by myelography. Operation was done in all three cases and varicosities were observed pressing on the nerve roots, but no evidence of a herniated disk could be found despite careful search. Pain was relieved in each instance.

The epidural veins in which the varices were encountered belonged to the primary system of veins which drains the spinal column and its adjacent musculature and meninges. This system, which is not accompanied by arteries and is without valves, is formed by large plexuses within and around the spinal column throughout its entire length. These spinal veins have been brought into clinical prominence by the outstanding work of Batson, who demonstrated their role in the spread of carcinomatous metastases from the prostate to the brain without pulmonary involvement.

Varicosities of the pial veins are usually found on the dorsal surface of the spinal cord subdurally and have been ascribed to obstruction to the return flow of blood at a higher level in the spinal veins. True congenital dilatations of the veins may also occur and may result in angiomas. On myelography the enlarged pial veins are enveloped by the pantopaque, producing channel-like radiolucent shadows where the opaque oil is displaced by the dilated vein or veins. Epidural varices may produce a myelographic appearance which cannot be distinguished from that associated with protrusion of the nucleus pulposus.

ELLWOOD W. GODFREY, M.D.

THE GENITO-URINARY SYSTEM

Studies in Urolithiasis: I. Composition of Urinary Calculi. Edwin L. Prien and Clifford Frondel. J. Urol. **57:** 949–991, June 1947.

In a study of 700 representative urinary calculi collected from practising urologists, the authors have applied the physical technics of mineralogy to identify the crystalline components. Since, with the exception of the extremely rare fibrin and bacterial types, all urinary calculi are crystalline, these methods are accurate.

The calculi were first fractured and dissected with a pointed tool under ordinary light, revealing structural characteristics such as texture, lamination, porosity, and individual crystal form. Samples were dissected from the nucleus and various layers and powdered for further study. The crystalline components are thus grossly identified.

Examination by polarized light is done by means of the petrographic microscope. Polarized light is influenced by transmission through transparent grains of coarsely powdered calculus and these changes in the light are measured by the microscope and may be recorded as the optical constants of the substance. The optical constants depend on the atomic structure and are distinct, invariable, and characteristic for any particular substance and constitute an accurate method of identification. It is possible to identify unknown compounds by comparing their optical constants with a prepared table of constants (listed in the bibliography) for known compounds. One milligram of the substance is sufficient for such an examination, which is quick and inexpensive. In the analysis of calculi composed of several components, it is possible to approximate the percentage (to within 5 to 10 per cent) of each component by powdering the entire calculus, mixing the fragments thoroughly and making grain counts in random samples through the petrographic microscope.

Examination by x-ray diffraction photography consists in irradiating very finely powdered calculous material by a beam of monochromatic x-rays and recording the rays diffracted (reflected) from the crystal planes (planes of atoms in the substance) upon a photographic film as a series of lines of variable spacing and intensity, producing what is known as a "powder pattern." Such patterns are characteristic for each substance. They are identified by comparing them with previously prepared patterns of known substances (master list from the American Society of Testing Materials). While x-ray diffraction study is not practical in routine analysis of calculi, because it is expensive and time-consuming, it is useful as affording a permanent graphic record for comparison with later studies. When dealing with mixtures, it is possible to identify the several constituents and to estimate the approximate proportions of each by the relative intensity of the superimposed patterns.

In this study, only 9 distinct crystalline substances were found: Calcium oxalate monohydrate, calcium oxalate dihydrate, magnesium ammonium phosphate hexahydrate, carbonate-apatite, hydroxyl-apatite, calcium hydrogen phosphate dihydrate, uric acid, cystine and sodium acid urate. These may be divided conveniently into the following groups: oxalates, phosphates, uric acid, urates and cystine. The appearance, associations, hardness, specific gravity and optical constants of these substances are given. A determinative table, photographs, x-ray diffraction photographs and x-ray spacing data are presented.

Pure calcium oxalate calculi constituted 36.1 per cent of the total; mixed calcium oxalate-apatite calculi comprised 31.0 per cent of the total. These calculi usually occur in acid sterile urine. Pure magnesium ammonium phosphate hexahydrate, pure apatite and mixtures of these two substances comprised 19.5 per cent of the total. These calculi usually occur in alkaline infected urine.

The authors believe that the methods of optical and x-ray crystallography provide powerful tools for the study of various aspects of calculous disease and hope that these may be valuable in attacking the problem of prevention of recurrent calculi.

DOUGLAS NAGLE, M.D.

Massive Calcinosis with Renal Insufficiency Due to Polycystic Kidneys: A Case Report. T. M. Burkholder and R. R. Braund. J. Urol. **57:** 1001–1009, June 1947.

The authors report an unusual case of chronic renal insufficiency and acidosis with bizarre calcium deposits about the joints, but with no demonstrable skeletal changes.

The patient was a forty-six-year-old white nurse who had enjoyed good health until four years prior to hospital admission, when she had an attack of substernal pain followed by nausea and vomiting which persisted for three weeks. At that time she was told that she had renal insufficiency due to polycystic kidneys. Following this initial episode, she enjoyed fair health until a few weeks before admission, when there was rapid enlargement of both shoulders accompanied by pain and itching. Other joints were similarly involved. Examination revealed subcutaneous cyst-like tumors varying from 2 to 23 cm. in diameter about many of the large joints. The kidneys were greatly enlarged and filled the whole abdominal cavity from the costal margin to the pelvis.

Roentgen studies of the shoulders showed dense deposits of calcium which obscured the heads of the humeri. Similar deposits in the gluteal regions obscured the heads of the femora. The hands, feet, skull, spine and long bones showed no evidence of cystic degeneration or osteoporosis.

Laboratory data were as follows. Urinalysis showed acid reaction, with numerous red blood cells microscopically. Blood urea nitrogen was elevated to 172 mg. per cent, creatinine 6.9 mg. per cent, and uric acid 9.2 mg. per cent. The CO_2-combining power was 31 volumes per cent. The serum phosphorus was elevated to 10.2 mg. per cent, serum calcium 11.5 mg. per cent, and alkaline phosphatase 5.4 Bodansky units.

The authors find the case difficult to classify. It did

not correspond closely to calcinosis circumscripta or calcinosis universalis. The patient showed no skeletal changes or bone destruction such as would be expected in metastatic carcinoma. Laboratory findings were in sharp contrast to those in primary hyperparathyroidism. It is concluded that the deposits of calcium salts in the neighborhood of the joints were probably the result of chronic acidosis and hyperphosphatemia induced by renal insufficiency secondary to polycystic kidneys.

RICHARD C. RIPPLE, M.D.

Crossed Ectopia with Fusion. Review of Literature and a Report of Four Cases. Benjamin S. Abeshouse. Am. J. Surg. **73:** 658–683, June 1947.

One of the relatively rare types of renal fusion anomaly is crossed ectopia with fusion. The author has collected 47 new cases published since Wilmer's report (J. Urol. **40:** 551, 1938) and has added 4 personal cases, bringing the total of reported cases to 337. He presents a study of the embryology of the urinary tract in considerable detail to give a better understanding of this anomaly.

The distinguishing feature of crossed ectopia with fusion is the congenital transposition of one kidney to the opposite side with fusion of the transposed kidney to the other. There are six anatomical varieties of this anomaly which, in the order of relative frequency, are (1) elongated (with ectopic kidney in inferior position); (2) sigmoid or "S"-shaped; (3) "L" (transitional form); (4) disk (fusion of medial borders); (5) lump (irregular fusion); (6) elongated (with ectopic kidney in superior position). Crossed ectopic kidney with fusion has been found at various levels from the lower thoracic vertebrae to a position deep in the pelvis. The renal components may show remarkable variations in size and shape. The outline of each kidney is preserved in the simpler fusion types, but marked irregularities are noted in the more complex types. Usually the ureter of the non-ectopic kidney descends in a normal fashion to enter the bladder on its proper side, whereas the ureter of the ectopic kidney crosses the mid-line and enters the bladder on the opposite side in its normal position in the trigone. Variations of this relationship occur, however.

The age and sex incidence of this condition is of little significance from an embryological or clinical standpoint. In the 337 cases reviewed, the sex ratio was four males to three females. The majority of the cases were seen in persons below the age of fifty years.

Associated renal pathological conditions were found in 204 of the 337 cases. A great variety of lesions were encountered. Among the more common were hydronephrosis of one or both kidneys, pyelonephritis, pyonephrosis, renal calculi, and nephroptosis.

There is no symptom-complex typical of this anomaly. The clinical picture is considerably modified by the size and location of the fused kidneys, the presence of associated pathological lesions within one or both renal components, and associated pathological lesions of a congenital or acquired nature in adjacent organs or structures. The predominating symptoms are pain, a palpable mass, and, less frequently, urinary disturbances.

The role this fusion anomaly as a cause of dystocia is mentioned. When the anomaly is situated at or below the promontory of the sacrum, dystocia is apt to occur.

The most important and reliable diagnostic procedure is pyelography. Cystoscopy alone is of little diagnostic value, as the ureteral orifices are normal in size and position. In the author's experience, retrograde pyelography permits a clearer and sharper delineation of the kidneys and ureters than excretory urography.

From the clinical standpoint, crossed ectopia with fusion has been confused with a variety of renal, intra-abdominal, retroperitoneal, and pelvic diseases. A complete urologic examination, including retrograde pyelography, would avoid this confusion and resultant errors in diagnosis.

The surgical treatment may be conservative or radical and is governed by the nature of the pathological lesion, the extent of the fusion deformity, and the condition of the patient. Conservative or palliative surgery can be undertaken with as little risk as in the normally formed kidney. Symphysiotomy combined with nephropexy may be employed with good results in cases presenting no significant pathological lesions but accompanied by pain of renal origin. Radical operation consists of removal of one renal component of the fusion anomaly, *i.e.*, heminephrectomy. This is the operation of choice in the majority of cases, for it insures a permanent cure by complete removal of the diseased component of the anomaly.

JOHN W. HOPE, M.D.

Ureteral Obstruction: Recent Advances in Its Embryology, Nosology and Surgery. David M. Davis. Brit. J. Urol. **19:** 71–82, June 1947.

Great progress has been made in recent years in elucidating the underlying pathology and the surgical repair of ureteral obstruction. The author emphasizes the fundamental importance of the relationship between obstruction and infection. Lack of recognition of this concept is explained by the following facts. First, many obstructions are slight, serving only to impede the flow of urine rather than arrest it completely, and therefore cause few or no symptoms. Secondly, such obstructions are often so difficult to demonstrate that many observers have come to believe that hydronephrosis is often due to neuromuscular disorders, developmental defects, etc., and not to obstruction.

Congenital ureteral obstructions are common. The diameter of the normal ureter is small and even a slight constriction interferes seriously with the proper conduction of the urine. In fetal specimens with narrowing and valve-like folds in the upper ureter, definite pyelectasis and caliectasis were already present, proving that hydronephrosis can occur before birth.

Aberrant blood vessels have been ascribed a predominant role in the causation of ureteropelvic obstruction. Such a vessel may be the sole cause of obstruction, but careful studies indicate that there is usually a ureteral narrowing in addition. This serves to explain the numerous instances in which division of an aberrant artery fails to cure a hydronephrosis.

It is noteworthy that large hydronephroses, usually due to congenital obstructions and therefore present from birth, cause no pain until the occurrence of infection. The very earliest danger signal here is usually a persistent or recurrent pyuria.

Since 1943, the author has recommended ureterotomy with intubation as the operation of choice in practically all cases of ureteropelvic and upper ureteral obstructions. In one case recorded in the present paper, the pelvis was entirely intrarenal and the stricture so close to the kidney that no type of pelvic operation was possible. In

another, a plastic operation was impracticable on account of the length of the stricture. In intubated ureterotomy reliance is placed upon the regenerative power of the ureteral epithelium to create a new and larger ureter molded about the splint tube. Regeneration occurs in from ten to twelve days. The surgeon is freed from dependence on sutures and no foreign material, except the splint tube, needs to be placed in the wound. Results are most gratifying.

M. WENDELL DIETZ, M.D.

Some Information Derived from the X-Ray Examination of the Neck of the Bladder and of the Prostatic Urethra. Athayde Pereira. J. Urol. **57:** 1054–1068, June 1947.

The author's technic for demonstration of the bladder neck and prostatic urethra differs somewhat from the conventional procedure. He uses barium sulfate as a contrast medium, 25 gm. dissolved in 100 c.c. of boiling water. About 60 c.c. of this solution, while still warm, is injected through the urethra. The entire urethral tract is filled in order to obtain a complete picture of the internal ring, and roentgenograms are obtained during the final period of filling. Anteroposterior and oblique projections are made with the patient in the horizontal or, in the case of adenoma, in the "half Trendelenburg" position.

In the interpretation of the films one must keep in mind the filling characteristics of the various urethral segments, the topography of the colliculus seminalis, stretching and deformities of the prostatic urethra, filling of the true prostatic glands, position of the internal ring in relation to the cavum vesicalis, configuration of the prominences of the basal plane of the bladder, and the appearance of the bladder outline itself.

The normal bladder neck is represented by an internal ring with two slightly protruding edges with the introitus looking toward the apex or slightly forward. The fringes undoubtedly represent a slight protrusion of the mucous lining. Their greater or lesser prominence and their relation to the neck result from the tonus of the sphincter of the neck. They are not very marked with hypotonus and the ring opens out; in hypertonic cases they become exaggerated and may even project unduly into the bladder cavity.

Under the heading "disectasias of the neck," the author includes hypoplasia of the internal ring, acquired and senile atrophy, and sclerosis of the neck. The appearance of the internal ring and changes in the prostatic urethra are more or less modified with each type. With an enlarged trigonal muscle, the posterior margin of the ring is seen in profile to be forward and overlapping the anterior margin, forming a kind of small valvular tongue. The picture is that of hypertonus, with enlargement and atony of the bladder; pulsion diverticula not infrequently occur.

Prostatic adenoma, as it develops, influences the appearance of the prostatic urethra. When the median lobe is involved, the inner ring turns forward, the nodule protruding behind the ring on the base of the bladder. The urethra elbows the portion above the verumontanum, its angulation conforming to the development of the adenomatous nodule. When there are lateral nodules protruding into the bladder, the prostatic urethra may become stretched, deformed, and enlarged. Interruption of the urethral image suggests angulation. Protrusion of a ventral or distal lobe adenoma may occur into the lumen of the enlarged and deformed prostatic urethra. In total adenoma, the lateral lobes stand out in profile x-rays and show an even or uneven growth to each side. The ring is turned upwards and the urethra here too becomes elongated, enlarged, and deformed. In the anteroposterior view, the image of the tumor is seen to bulge at the base.

Prostatic cancer, like prostatic adenoma, is a progressive disease, with a variable x-ray aspect. Early in the course, the prostatic urethra is slightly elongated, but this is not specific. When the growth of the tumor is in a subvesical direction, no protrusion inside the bladder is detected. The whole tract of the prostatic urethra may narrow progressively, but in some cases it undergoes no change. When the tumor develops in the direction of the vesical cavity, the protrusion differs from that of adenoma in being lobulated and irregular. When adenoma coexists with cancer, the features are those of an adenoma. The adenoma almost invariably is located in the upper vesical part of the tumor, while the cancer is in the subvesical part, near the colliculus seminalis.

DAVID S. MALEN, M.D.

RADIOTHERAPY

Cancer of the Thyroid. Hugh F. Hare. Surg. Clin. North America **27:** 561–563, June 1947.

As an introduction to his paper, the author presents Shields Warren's classification of thyroid tumors:

Benign

1. Adenoma
   - *a.* Embryonal
   - *b.* Fetal
   - *c.* Simple
     - (1) Hürthle cell
   - *d.* Colloid
2. Papillary cystadenoma
   - *a.* Originating from thyroid
   - *b.* Originating from aberrant thyroid

Malignant

Group I. Low or potential malignancy
1. Adenoma with blood vessel invasion
2. Papillary cystadenoma with blood vessel invasion
   - *a.* Originating from thyroid
   - *b.* Originating from aberrant thyroid

Group II. Moderate malignancy
1. Papillary adenocarcinoma
2. Alveolar adenocarcinoma
3. Hürthle-cell adenocarcinoma

Group III. High malignancy
1. Small-cell carcinoma (carcinoma simplex)
   - *a.* Compact type
   - *b.* Diffuse type
2. Giant-cell carcinoma
3. Epidermoid carcinoma
4. Fibrosarcoma
5. Lymphoma

At the Lahey Clinic, of 240 patients with malignant tumors seen between the years 1926 and 1936, 108 (45 per cent) belonged to the low or potentially malignant

group. The author's studies indicate that in most instances lesions of this group arise in pre-existing tumors of the thyroid, usually in single adenomas without evidence of toxicity, from which it readily follows that single adenomas of the simple type should be treated by surgery followed by irradiation. The distinguishing diagnostic point between thyroiditis and carcinoma of the thyroid is that in the latter the symmetry and contour of the gland are lost while in thyroiditis the gland remains symmetrical. Since carcinoma or malignant change in a thyroid adenoma may occur at any age and in a tumor of any size, the patient's age and the size of the lesion at the time of examination are not diagnostic criteria. It is of interest that tumors arising in lateral aberrant thyroid tissue were sometimes mistaken clinically for tuberculous adenitis.

It is worthy of note that malignant disease of the thyroid is seldom found in the toxic adenoma. In the ten-year period reviewed, only 7 such cases were found.

The roentgenogram is of little significance in determining the presence of malignant change within a tumor unless there is secondary invasion of the trachea or pulmonary involvement. Because of the frequency with which the lung is involved, however, it is considered necessary in all cases of suspected thyroid cancer to obtain roentgenograms of the trachea and chest prior to treatment.

Surgery should be carried out in all cases of thyroid tumor, first to remove all the tumor possible and second to free the muscles of the neck so as to eliminate danger of compression of the trachea from edema following heavy irradiation. In some cases where infiltration has taken place into the thyroid muscles, it is necessary that a tracheotomy be done before radiation therapy is carried out. The author has given a total of 2,000 r to each of three fields, measuring 7 × 10 cm., each field receiving 150 r daily. The treatment factors were 200 kv., 1.0 mm. Cu and 1.0 mm. Al filtration, h.v.l. 1.3 mm. Cu, distance 50 cm., 24 r per minute. Radiation dermatitis almost invariably follows this treatment, but only one case of actual slough has occurred in the author's experience.

The five-year survival rates for 231 cases treated by surgery and radiation are as follows:

	Per Cent	
Fetal adenoma	71	45% of total
Papillary cystadenoma	62	
Papillary adenocarcinoma	80	
Alveolar adenocarcinoma	27	
Small-cell carcinoma	22	
Giant-cell carcinoma	17	
Fibrosarcoma	33	

SYDNEY F. THOMAS, M.D.

Treatments of Inoperable Cancer of the Larynx with X-Ray after Preliminary Surgical Removal of the Thyroid Cartilages with Improved Classification of the Larynx. Millard F. Arbuckle. South. M. J. **40:** 462–465, June 1947.

The author believes that a laryngofissure is the treatment of choice when dealing with cancer of the true vocal cords. This operation gives a lasting cure in about 83 per cent of these cases. When cancer has extended beyond the limits of the true vocal cords, we cannot consider the lymphatics free of invasion, and in such instances a laryngofissure will not suffice. The surgeon should, therefore, institute x-ray therapy immediately after the patient has recovered from the effects of the operation, if he suspects lymphatic involvement. The lymph nodes do not have to be palpable to be involved. Microscopic examination of the nodes of the jugular sheath are a good criterion for spread to the lymphatics.

The author classifies cancer of the larynx in two groups: (1) cancer of the true vocal cords and (2) all other cancers of the larynx. He recommends that patients of the second group be treated by the institution of x-ray therapy after a preliminary removal of the thyroid cartilages by subperichondrial resection. The operation does not result in collapse of the larynx or interference with the voice or respiration. The purpose of the procedure is to allow intensive x-ray therapy without killing the thyroid cartilages and subjecting the patient to the dangers of subsequent suppuration. The x-ray dosage has not been established.

Case records of 16 patients treated by this method are included. The results seem favorable.

JOHN DECARLO, M.D.

Carcinoma of the Breast: Results of Combined Treatment with Surgery and Roentgen Rays. Samuel F. Marshall and Hugh F. Hare. Ann. Surg. **125:** 688–702, June 1947.

At the Lahey Clinic (Boston) radical mastectomy (usually without irradiation) for cancer of the breast, in an earlier series of cases, gave 38.6 per cent five-year survivals. Since it was felt that these results could not be greatly improved by variations of surgical procedure, the authors began in 1935 to supplement operation with postoperative roentgen therapy. During the period 1935–41, 238 patients were treated by radical mastectomy followed by intensive irradiation. No attempt was made to confine treatment to a selected group of cases, but all those in which the carcinoma was confined to the breast and the corresponding axilla were included. In 62 per cent of the group there was pathologic evidence of axillary extension.

The operative procedure is similar to that used elsewhere. Early ambulation, early use of the arm, and early institution of roentgen therapy are emphasized. Irradiation is usually begun within ten to fourteen days postoperatively. The factors are: 200 kv.p., 50 cm. distance, 1.0 mm. Cu filter, round ports measuring 15 cm. An initial dose of 300 r is given to each port—supraclavicular, axillary, and scar areas—one port being treated daily. After the third day, each of the three ports receives 100 r daily, for a total dose per port of 2,400 r. All dose measurements are in air. The erythema produced was not excessive in any instance, and no local treatment other than vaseline or boric acid ointment was required. The patients are checked for skin reactions three weeks after completion of treatment and again at eight weeks. On the latter occasion fluoroscopy is done to rule out radiation pneumonitis, which the authors believe they have avoided by use of small daily doses. Roentgen sickness is handled by reducing daily dosage further or by allowing rest periods when necessary.

Radiation therapy has also been used for palliation in the presence of skin recurrences and metastases in the nodes, bones, or abdomen. Radiation therapy is preferred to surgery for recurrent skin nodules since surgery does not tend to block off the adjacent lymphatics as does irradiation.

The authors have not found estrogenic substances and testosterone of particular value. Roentgen sterilization in premenopausal cases appears to be most useful in patients with increased pain in the areas of metastasis and pain and swelling of the remaining breast during the menstrual periods.

Of the 238 patients who underwent radical operation followed by irradiation, 52.1 per cent have survived five years or more without evidence of recurrence as contrasted to the earlier figure of 38.6 per cent before postoperative roentgen therapy was employed routinely. The authors seem convinced that most of this improvement in results is due to the addition of roentgen therapy.

B. S. KALAYJIAN, M.D.

Cancer of the Cervix. Bellevue Hospital Method of Treatment Over a Period of Twenty-one Years. Ira I. Kaplan and Rieva Rosh. Am. J. Roentgenol. **57:** 659–664, June 1947.

Because Bellevue Hospital (New York) is a large municipal hospital, few early cancer cases are seen there. In nearly one-third of the cases of carcinoma of the cervix, involvement was so extensive at the first examination that the patients were immediately transferred elsewhere for custodial care. The present report is based on 916 treated cases.

Since 1934 all gynecologic tumor cases are examined by both the Radiation Therapy Service and Gynecological Department, to determine the proper method of treatment. When irradiation is deemed advisable, the patient is taken over for treatment by the Radiation Therapy Department. External irradiation precedes radium application, 1,800 to 2,000 r (measured in air) being delivered to each of four pelvic ports, at 200 kv.p., through 0.5 or 1 mm. Cu or Thoraeus filter. Radium is applied with a rubber colpostat to both the uterine canal and cervix, except where previous hysterectomy has been done. The radium dosage is approximately 7,000–8,000 mg. hr., 4,500 mg. hr. to the cervix and the rest to the uterus. In cancer of the cervical stump, the type of radium therapy applied depends upon the condition present and the character of the previous operation.

From their large experience of over twenty-one years the authors feel that irradiation is the best method for the treatment of cervical cancer, as even in Stage IV cases the disease is often controlled and life is prolonged in comfort. They report 179 of 916 patients alive for five years or longer.

ELLWOOD W. GODFREY, M.D.

Intravaginal Radiation Therapy. John S. Bouslog. Am. J. Roentgenol. **57:** 665–670, June 1947.

From a study of autopsy material, the author came to feel that in view of the potential variations of location of the cervix and uterus there could be no standard method of radium application from the vaginal surface. The goal is to obtain uniform irradiation to all cancer cells throughout the pelvis. In addition, the dosage received must equal the minimal lethal dose, and if it exceeds this, the excess must not be beyond the normal tissue tolerance.

The ideal method is to concentrate the radiation upon the particular organ. Such concentration of energy can be assured only by the most exact orientation of the organ's position in the individual patient. Therefore, it is necessary in each case to determine both the position of the lesion as projected upon the surface of the body in relation to certain fixed points and its depth from the surface. For intravaginal therapy the pelvis is divided into five fields: two anterior, two posterior, and one perineal. The author uses a perineal field, as he feels that more radiation may be delivered to the cancer site than can be delivered through lateral fields over the hips, and also because radiation over the lateral fields may affect the bony structures causing changes which may result in pathologic fracture.

In each case external irradiation is given before the radium or intravaginal therapy in order to try to stabilize the cancer cells and prevent any lymphatic extension. Administering the external irradiation usually requires about three weeks, as it entails using 200 kv. technic and giving 250 r daily for a total dose of 1,000 r over each field. Intravaginal therapy is started before the reaction begins in the perineal area so that the tissues are not too tender for the introduction of the vaginal cones. Both external irradiation and intravaginal therapy should be repeated in four to six weeks. Over 5,000 r delivered to the site of the cancer in three months may elicit a delayed reaction; that is, an ulceration, increased discharge, and occasionally some bloody mucus. This is controlled by local treatment.

In summarizing, the author concludes that it must be borne in mind that there is no one method of treating all cases; each must be carefully analyzed, evaluated, and the method chosen which offers the best result.

ELLWOOD W. GODFREY, M.D.

Carcinoma of the Cervix. An Applicator for Greater Parametrial Dosage. Lloyd A. Campbell. Am. J. Roentgenol. **57:** 697–702, June 1947.

The author describes a uterine applicator which, following administration of a total dose of 7,200 mg. hr. in two applications of thirty-six hours each with a four-day interval, delivers 5,970 gamma roentgens to a point 2 cm. lateral to the internal cervical os, 3,990 gamma roentgens at 3.5 cm., and 2,500 gamma roentgens at 5 cm. This provides 2.5 threshold erythema doses to the lateral parametrial areas which, together with adequate external radiation, will closely approximate the 6 threshold erythema doses necessary to control the disease.

The applicator consists of a circular body to which is attached the cervical tandem and two stationary capsules placed 2.5 cm. apart. These capsules are 1.8 cm. in length with a diameter of 0.75 cm. and, like the tandem, have a filter equivalent to 1.0 mm. of platinum. The placing of the stationary capsules 2.5 cm. apart contributes to the dosage given to the cervix in a manner similar to that of the colpostats or other multiple sources used in several of the established technics. Within the body of the applicator is located a cam which actuates dual racks or lateral arms, to each of which is fixed a capsule or radium source. These capsules are 2.5 cm. in length with a diameter of 1.0 cm. and have a filter equivalent to 1.5 mm. of platinum. By the rotation of the cam, these capsules can be extended laterally any distance up to 7.5 cm. in total width, and in approximately 70 per cent of cases no difficulty was encountered in obtaining this maximum width.

The author feels that this method presents the advantage of simplicity, accuracy of placement, absolute immobilization, and greater parametrial dosage.

ELLWOOD W. GODFREY, M.D.

Radium Therapy of Hemangio-Endothelioma of the Uterine Cervix. Harry H. Bowing, Robert E. Fricke and James T. McClellan. Am. J. Roentgenol. **57:** 653–658, June 1947.

The authors report four cases in which a hemangio-endothelioma occurred in or on the cervix, these being the first cases, to their knowledge, reported in this location. The most prominent symptom in each instance was bleeding, with little or no vaginal discharge. The tumors seemed very radiosensitive, with excellent response to irradiation therapy.

ELLWOOD W. GODFREY, M.D.

Complications Following Radiotherapy of Carcinoma of the Cervix Uteri. Walter L. Thomas. South. M. J. **40:** 467–471, June 1947.

There are six main groups of complications following radiotherapy for carcinoma of the cervix. (1) Skin complications, such as ulceration, telangiectasia, and cancer are extremely rare when the radiation is administered in fractionated doses. (2) Blood complications, as leukopenia, are also unusual, but it should be recalled that many of the patients are anemic prior to the institution of treatment as the result of excessive vaginal bleeding, and this anemia should be corrected prior to irradiation. (3) Vaginal complications, as adhesive vaginitis, fibrosis, and sclerosis, are common and should be combated by manual and prosthetic dilatations. (4) Bladder and ureteral complications—ulceration, telangiectasia, and fistula—do not appear until a year after treatment unless the radium has been poorly placed. Urologic follow-up is indicated in searching for possible lower ureteral obstruction with resulting hydroureter and hydronephrosis. (5) Rectal complications are the most frequent and troublesome of the reactions. A proctitis usually develops during the course of treatment, particularly if intravaginal irradiation is employed. Five per cent of cases show the late and serious complication of fibrosis and ulceration, which may be limited to the rectal wall or may involve the perirectal tissues. Stenosis, stricture and occasionally fistula follow. The pain is frequently more intractable than that caused by the carcinoma, so that chordotomy or lumbar sympathectomy must be undertaken. Hemorrhage is also a serious result and this is treated with saline enemas and rectal oil instillations. (6) Pelvic infections are serious complications, frequently unavoidable and carrying the highest early mortality. External and vaginal irradiation employed before radium applications aid in diminishing and eliminating localized infection. Pyometra is to be prevented by maintaining the patency of the cervical canal with sounds and dilatators. Parametritis, with or without peritonitis, is combated with sulfanamides and penicillin. Pelvic cellulitis is usually a late result and should not be confused with extension of the carcinoma.

FRANCIS F. HART, M.D.

Irradiation Reactions in the Bladder: Their Occurrence and Clinical Course Following the Use of X-Ray and Radium in Treatment of Female Pelvic Disease. Ernest M. Watson, Charles C. Herger, and Hans R. Sauer. J. Urol. **57:** 1038–1050, June 1947.

In the study of the records of 5,990 patients treated for cancer or fibromyoma of the uterus, irradiation reactions in the bladder were discovered in 164, or 2.74 per cent. There were 4 acute and 160 late reactions.

Acute irradiation reactions occur during or shortly after treatment with x-radiation, especially when this has been preceded by radium application. The reaction is in the nature of an epithelitis and is manifested clinically as a cystitis of varying degree. Treatment is conservative, consisting in the use of mild antiseptics, discontinuation of irradiation, and sedation. Sulfonamides are contraindicated. Most of these acute reactions will subside in a relatively short time.

It is generally agreed that late irradiation reactions are due to prior treatment with radium rather than to roentgen rays. These "late radium reactions" are manifested by painless hematuria in the milder cases and by dysuria and/or frequency, often in combination with hematuria, in more severe cases. The authors describe three grades of late reactions, all characterized by telangiectasia, ulceration, and edema. All are localized lesions developing almost invariably in the lower posterior bladder wall. The most severe reactions, Grade III, present a clinical picture dominated by a variety of complications. Extensive tissue necrosis and infection are the rule. Passage of gravel and stones is a frequent finding. Occasionally fistula formation occurs because of extensive necrosis. Partial or complete obstruction with occasional ascending urinary infection may develop. Treatment of "late radium reactions" is based upon the control of infection and the prevention of the various complications as required in the individual case.

Late radium reactions were first differentiated from atypical bladder tumors by Dean (J. A. M. A. **89:** 1121, 1927). The importance of distinguishing these lesions from carcinoma, which they frequently resemble, is obvious, as ill-advised methods of treatment, as electrocoagulation, further irradiation, or surgery, may add to the damage. The distinction may, however, be difficult, even histologically, since the margins of the ulcerated areas may show epithelial inclusions separated from the bladder epithelium and having irregular cells with mitotic figures.

The authors attribute late irradiation reactions to a combination of the following factors: (1) excessive irradiation; (2) variations in individual tolerance; (3) anatomical variations in thickness of layers formed by cervical or uterine canal and bladder wall; (4) faulty technic in the application of radium. An attempt was made to correlate the amount of radium radiation delivered and the severity of late radium reaction in the bladder, and a table is presented setting this forth. The authors conclude, however, that the amount of radiation employed had practically no influence on the intensity of the lesion, except in 5 patients who received more than 10,000 milligram hours; in these patients most of the reactions were of the severe type. [Such a tabulation would seem to be of little value unless considerably more data were included, such as type of radium applicator, size of the original lesion, and distance of the radium from the posterior bladder wall. J.C. K.]

The time elapsing between radium application and onset of the lesion was charted and it was found that half the lesions appeared about two years after treatment and that 75 per cent appeared within the first four years. The authors suggest that the incidence of late radium reactions is probably higher than can be determined because many patients die before reactions become apparent, and in other, lesions develop which are never discovered.

JAMES C. KATTERJOHN, M.D.

A Comparison of Radiation and Surgery for Cancer of the Bladder. Victor F. Marshall. J. A. M. A. **134:** 501–507, June 7, 1947.

Strict comparison between surgical and radiation methods in treatment of cancer of the bladder is not possible, since radiation cases, in general, are unselected, whereas in a surgical series the local status in the genito-urinary tract, as well as the general condition of the patient, makes some selection necessary even when palliation is the objective. Three hundred consecutive cases of neoplasm of the bladder occurring from 1932 to 1938 on the Cornell service of the New York and Memorial Hospitals (New York) were treated by irradiation. Implantation of gold radon seeds averaging 1.5 millicuries each into the base of the tumor and an area 1 to 2 cm. wide of normal appearing tissue surrounding it followed excision of the superficial portion. Technical considerations decided whether implantation was cystoscopic or through a suprapubic cystotomy, although the latter approach favors accuracy in placement. A dose of 2,000 r was delivered to each of six large pelvic ports (200–250 kv.; 50 to 70 cm. focus skin distance). Recurrences were treated by either (or both) roentgen or radon irradiation.

By the radiation methods used, 17 per cent five-year survival was obtained, while 80 per cent of the patients were dead of the disease or its complications. Twenty-seven patients, or 9 per cent, were alive and by fair evidence free of neoplasm after five years. Strict criteria applied by the author reduce this figure to an indisputable 6 per cent. Complications, some requiring unforeseen operations, were common in the treated group. Cystitis, lasting months or years, was present in the majority, while contracted bladders, calcific incrustations, and vesical calculi were not unusual. Radiation proctitis, incontinence, skin ulcerations, and edema of the genitals were less common; 2 patients had fecal fistulas, and in 4 communications developed between bladder and vagina.

While for untreated patients with neoplasm of the bladder the average survival time from diagnosis approximates nineteen months, in 287 patients of this series with a follow-up of three years or more, the average survival time was twenty-seven months. The average life expectancy of a similar population group is fifteen years.

Surgical treatment of bladder tumors ranges from simple cystoscopic fulguration to partial resection and total excision with transplantation of ureters. Infrequently a cure is effected when a small and superficial, usually low-grade, tumor is fulgurated, but the difficulty in selecting such cases is imponderable. In a group of 33 patients treated by partial resection, the average survival time was twenty months, a figure close to that of the untreated group. However, a more complete follow-up might have raised the survival time for this group. Cystectomy imposes the additional hazard of ureteral transplantation, and in this group of 72, 48 are still alive. Since 45 of the 48 patients were operated on within the past five years, evaluation of the five-year survival rate is incomplete. However, thus far the smallest possible rate would be 43 per cent and the author considers this as favorable in comparison with survival rate of 6 per cent in the longer studied group treated by irradiation. Combinations of radiation and surgical methods may offer more than either alone.

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Cerebral Contusion: Post-Concussion Syndromes; Roentgen Therapy. Manuel F. Terrizzano and Arturo J. M. Terrizzano. Radiología (Buenos Aires) **8:** 138–142, May–December 1945.

For a long time the term *commotio cerebri* has been utilized to denote the complete neurologic factor, of a transitory character, following traumatism. The diagnosis is based upon a triad of symptoms: (1) loss of consciousness, (2) retrograde amnesia, and (3) transitory lymphopenia. To these basic signs should be added headache, migraine, vomiting, nausea, and mental fog.

As to the mechanism of the action of roentgen rays in these cases, the authors believe irradiation produces, as in other processes of trophic nature, truly vascular shock. Vasodilatation occurs after irradiation through a sort of paralysis of vasoconstrictors. This is followed by the re-appearance, although in diminished degree, of the excess of contractile tone. This series of alternations of true vascular kinesia brings about an equilibrium of the motor function which presides over the metabolism and proper neurocellular function.

The authors irradiate the skull through four ports, with fields 10 × 10 cm., anterior, posterior, and lateral, giving 140 to 320 r (in air), at 200 to 400 kv., at each treatment, so that each of the four areas receives this dose once a week. The more recent the beginning of the process, the smaller the dose employed. The series is usually not repeated in less than six to twelve weeks.

The authors have treated 10 cases, in 7 of which distinct improvement was obtained. One case, treated five years after traumatic shock, was not modified in the least, and the 2 remaining cases are still under treatment. Case histories are given in detail.

JAMES T. CASE, M.D.

Stimulating Roentgen Therapy in Ovarian Insufficiency. José Luis Molinari and Fidel Maria Diaz. Radiología (Buenos Aires) **8:** 134–138, May–December 1945.

Among the unsolved problems in the field of biologic action of radiation, one of the most interesting is that of the exciting or stimulating effect of the rays, an effect denied by some investigators and accepted very definitely by others. The majority of writers, including the present authors, tend to admit this effect, believing that the x-rays, in common with other therapeutic agents, obey the general law of Arndt and Schulze, which states that a given therapeutic agent acts as a stimulator in weak doses; as an inhibitor with average doses; and with destructive effect in high doses.

The authors speak of a direct exciting action and an indirect exciting action. The former affects the structure of the cellular colloids in an essentially more destructive manner. The indirect exciting action may result from a local hyperemia, some vasodilation, produced by the irradiations. The great sensitivity of the ovaries to roentgen irradiation has been recognized for more than forty years, but still it has not been explained. The effect is presumed to be due to biochemical alterations which have not yet been determined.

Roentgen therapy administered over the hypophysis likewise has a stimulating effect on the ovaries. The authors quote many of the early writers, but apparently do not add any new experimental observations to sustain their thesis as to the efficacy of such treatment.

Of 218 patients treated by the authors, 75 have been followed. Of these, 59 were brought to normal or improved menstrual function; 16 were failures. In 42 patients in whom irradiation was given over the ovaries, success was attained in 83 per cent; of 33 receiving simultaneous hypophyseal and ovarian irradiation, 72 per cent showed a favorable result. The authors utilized 180 kv., 6 ma., 0.5 to 1.0 mm. Cu filter, at a distance of 40 cm. Treatment is given over a three weeks period. The first week an anterior pelvic field, 20 × 24 cm., receives 100 r measured in air; and right and left hypophyseal fields 80 r each. The three fields are treated at one session. The second week the posterior pelvic field, 20 × 24 cm., receives 100 r and the two hypophyseal fields 80 r each, given in one session; the third week the first treatment is repeated. Thus the patient receives a total of 240 r to the hypophysis and 300 r to the pelvic region, measured in air.

The authors express surprise that there is not more general acceptance of stimulating roentgen therapy in ovarian insufficiency. They are convinced of its great, sometimes spectacular, value.

JAMES T. CASE, M.D.

Qualities of the Roentgen Ray in Deep Therapy. Federico Vierheller. Radiología (Buenos Aires) 8: 115–133, May–December 1945.

The author demonstrates the great influence of the focus-skin distance on the intensity of radiation in the depth of the irradiated body. Theoretically and by physical measurements he determines the fact that the liberation of the electrons as a basis of the biological effect reaches a maximum with a tension in the tube in the vicinity of 200 kv. He describes the phenomena of absorption and dispersion which equally demonstrate that it is hardly worth while to augment the tension. He believes that he has demonstrated that the dose increases in a high degree only with the increase of the focal distance. He recommends, therefore, the use of tensions no higher than 180 to 200 kv., with a filtration of 0.5 to 1.0 mm. Cu only, with a focal distance up to 80 cm., and with as high a millamperage as possible. For this he urges the manufacturers of x-ray generators to construct apparatus giving a maximum of 200 kv. but up to 30 or even 50 ma. in order to shorten the time of exposure in using the larger focal distance.

JAMES T. CASE, M.D.

RADIATION EFFECTS

Induction of Leukemia in Eight Inbred Stocks of Mice Varying in Susceptibility to Spontaneous Disease. Arthur Kirschbaum and Harry W. Mixer. J. Lab. & Clin. Med. **32:** 720–731, June 1947.

The incidence of spontaneous leukemia in inbred mice is dependent on the genetic constitution of the strain. If a chemical or physical agent is to be considered "leukemogenic," then its administration must result in (1) an increase in the incidence of leukemia among test as compared with control mice of the same stock, (2) an accelerated onset of the disease, or (3) both.

Studies are reported with three agents regarded as leukemogenic by the foregoing criteria: methylcholanthrene, estrogen, and x-rays. Methylcholanthrene (an 0.25 or 0.5 per cent solution in benzene) was painted on the skin; the estrogen was given in the form of a subcutaneous pellet of "estrone"; the x-rays were administered by total body irradiation (140 kv., at 30 cm. with 2 mm. Al filter). Eight strains were tested and the results are presented in a series of tables and charts. While all three agents used were capable of inducing leukemia in mice, the effectiveness of each depended upon the genetic constitution of the stock involved. Of the three agents, x-ray was the only one which might be considered to be almost universally leukemogenic for mice, but response to irradiation varied from strain to strain.

All three agents also induced cancer of various types in the experimental mice. It is pointed out that the fact that carcinogens also proved to be leukemogens lends support to the idea that leukemia is a neoplastic disease.

SYDNEY F. THOMAS, M.D.

A Quantitative Analysis of the Direct and Indirect Action of X Radiation on Malignant Cells. Ilse Lasnitzki. Brit. J. Radiol. **20:** 240–247, June 1947.

Tissue cultures of mouse adenocarcinoma 63 and tumors *in situ* were exposed to equal sublethal doses of x-radiation. The effects as indicated by mitotic and degenerating cell counts were compared.

Mitosis is absent in both culture and tumor eight minutes after exposure. It reappears at three hours *in vivo* but not for two days *in vitro*. In both cases most of the mitoses were abnormal. There is also an increase in cell size in both cases, but this appears earlier and more prominently *in vitro*.

Degenerating cells appear soon after irradiation in both tumors and cultures and are slightly more numerous *in vivo* than *in vitro* on the first day. From the second day to the seventh a marked increase occurs *in vivo* but not *in vitro*.

In irradiated tumors a slight dilatation of blood vessels appears almost immediately after irradiation. After twenty-four hours, the dilatation is marked and rupture with extravasation of blood is observed. These changes increase up to the fourth day. At ten days some capillaries show thickening of the intima.

These observations indicate that the primary effect of irradiation is a direct one and is qualitatively and quantitatively similar in both tumors and cultures. The higher count of degenerating cells in the tumor, with the observed changes in circulation, indicate that there is an important indirect effect related to circulatory changes in the host. Quantitative counts indicate that about one-third of the total effect is direct and two-thirds is indirect.

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